

I N T R A M U R A L A N N U A L R E P O R T

NATIONAL INSTITUTE ON AGING
NATIONAL INSTITUTES OF HEALTH

October 1, 1987 - September 30, 1988

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ANNUAL REPORT OF THE OFFICE OF THE SCIENTIFIC DIRECTOR

NATIONAL INSTITUTE ON AGING

The Scientific Director, NIA is responsible for the quality and direction of research undertaken by the Intramural Research Program. In addition, the Office of the Scientific Director (OSD) includes selected central administrative and support functions essential to the program's efficient operation. The organizational units which comprise the OSD are the immediate office of the Director, Administrative Services (Administrative Office and Procurement), the Public Information Office, and the intramural Personnel Office.

This year was one of transition in the Intramural Research Program. Dr. Richard C. Greulich, who had served as Scientific Director since 1977, retired at the end of March 1988. A search committee to help select a replacement had completed its work as of this writing and the final selection of the new Scientific Director is expected by early in the new fiscal year. Dr. Gunther L. Eichhorn, Chief, Laboratory of Cellular and Molecular Biology, was named Acting Scientific Director in the interim.

Also, this summer the sudden death of Dr. Bertram Sacktor, Chief of the Laboratory of Biological Chemistry for more than 20 years, came as a great shock to the entire NIA staff. Fortunately, Dr. Jeffrey Froehlich, a section chief in the laboratory, was able to assume a leadership role as acting chief. Currently, the laboratory is operating most efficiently under three research groups--regulatory mechanisms, mineral metabolism, and membrane biology.

The NIA Board of Scientific Counselors met twice during FY 1988, reviewing the Laboratory of Behavioral Sciences in October 1987, and the Laboratory of Personality and Cognition in May 1988. The Board meets again in November of this year at which time they will review the research activities and directions of the Laboratory of Molecular Genetics.

Staff of the IRP have continuing contacts with the Tokyo Metropolitan Institute of Gerontology (TMIG) in accordance with a memorandum of agreement between the NIA and the Japanese government. A second joint symposium between the TMIG and NIA is scheduled for November 1988 at the NIA's Gerontology Research Center in Baltimore. Both institutions will have seven or eight representatives speak on the general theme of "Aging and Disease." Dr. George Roth of NIA will serve as its coordinator, and Dr. Akio Sako will perform this function for TMIG.

Complete descriptions of research accomplishments in the various Laboratories and Branches can be found in later portions of this report, however, some of the most interesting highlights for the IRP are worth mentioning here.

○ Metabolism Section scientists' analyses of dietary intakes in the Baltimore Longitudinal Study of Aging (BLSA) population over a 20-year span (1960s-present) indicated that longitudinal dietary changes, which subjects voluntarily initiated between the 1960s and 1970s, continue at a comparable pace in the 1980s.

Notable changes included a further decrease in calories from fat, and increases in P/S ratio and in fiber intake. These changes were noted in young, middle-aged, and elderly study subjects.

- o A Laboratory of Behavioral Sciences study demonstrated that an internist/geriatrician and a nurse practitioner, working in a traditional office practice, can effectively treat elderly, non-demented, ambulatory, incontinent patients. Twenty-seven outpatients with symptoms of stress, urge, or mixed fecal and urinary incontinence, were able to effectively reduce their incontinent episodes by about 80 percent using biofeedback or habit training techniques. This study shows that behavioral treatments of urinary incontinence can be extremely cost effective since they can be implemented in an office setting without the need for expensive urodynamic evaluations.

- o Investigators in the Laboratory of Personality and Cognition found that when age, education and obesity were taken into account, only concept problem-solving was related to the concentration of glucose in the blood two hours after ingestion of a glucose load. Concept problem-solving is a measure of abstract reasoning and one of many measures included in analyses relating cognitive performance to glucose tolerance in BLSA female participants. For women in their sixties, better glucose regulation was associated with higher problem-solving performance. For women over 70, performance was not related to the glucose tolerance measure either for the entire group or for a healthier subgroup. These results suggest evidence that glucose regulation affects abstract reasoning in the elderly individual is weak and inconsistent.

- o Two age studies of sentence learning and forgetting were completed this year, representing six year repeat data on more than 200 BLSA men. When young and older adults were given the same opportunity to learn many sentences, findings reported in the literature—young adults perform better than older persons—held up. Age differences were maintained 3, 6 and 24 hours after learning of sentences. The amount of forgetting was equivalent for the two age groups. However, when the older age group was given more time to study each sentence, learning was similar for the two age groups and the older group did not forget more than the young even up to 24 hours after learning. These results provide further evidence that, for newly learned verbal material which is not mastered, forgetting is not age-related.

- o Laboratory of Cardiovascular Science analysis of 2-dimensional echocardiograms in normotensive BLSA subjects has shown that the age-associated left ventricular (LV) hypertrophy, reported previously by the same laboratory, is mediated largely by an increase in systolic blood pressure (SBP) which is seen with advancing age. When radionuclide-derived LV volumes and echocardiographic LV wall thicknesses are adjusted for body surface area and SBP, there are no distinct differences between men and women in cardiac structure or function.

○ Scientists in the Inorganic Biochemistry Section study the uptake and distribution of various metal ions with cellular in vitro age in human diploid fibroblasts. Recently, atomic absorption measurements of copper, aluminum and manganese have shown an approximate 2-4 fold increase of these metals in cells with aging, which is similar to that previously demonstrated with zinc. This increase is significant since it is much greater than the concomitant increases in cell volume, protein or RNA.

○ Investigators in the Endocrinology Section found that fat cells in culture secrete a differentiation factor which promotes the adipose conversion of islet-derived cells which are highly committed adipocyte precursors. This factor, a regulator of adipocyte development, has potential importance for studies of obesity.

○ An extramural collaborator evaluated the testosterone:2-hydroxypropyl-beta-cyclodextrin preparation, developed by investigators in the Macromolecular Chemistry Section. This preparation may be used to obtain a "burst-like" increase and fall in circulatory concentration of testosterone. Working with senescent rats, the collaborator Dr. George T. Taylor, found that (1) this new preparation improves the "maleness" behavior pattern; (b) prostate development is much less than with currently used testosterone ester preparations; and (c) the cyclodextrin preparation not only inhibits spermatogenesis, as other preparations do, but actually stimulates the process.

○ NIA Laboratory of Neurosciences investigators performed quantitative computer tomography (CT) on 64 healthy men and 43 healthy women. The results showed that the women had smaller lateral ventricular volumes at any age, even after normalization for cranial volume. In each sex, there was a significant increase with age in the volumes of the third and left and right ventricles, which was nonlinear and most pronounced in the later decades. The relation with age was the same for both men and women. These results demonstrate brain atrophy with aging in both sexes and show that, in studying disease with quantitative CT, sex matched controls must be employed.

○ Interferon, which has anticancer and antiviral activities, is a protein which is prevented from entering the brain by the blood-brain barrier. Laboratory of Neurosciences scientists this year gave intravenous injections of human lymphoblastoid interferon to rats. Following injection, alpha-interferon was found in all of the tissues but brain. However, osmotic barrier opening with intracarotid 1.8 molal arbinose caused significant brain uptake. The use of this method in humans may prove valuable for testing encephalitis from rabies or the AIDS retrovirus, or for primary brain tumors with an intact blood-brain barrier.

Overall, in calendar 1988, IRP scientists have published over 60 papers in the scientific literature, again proving their productivity as part of the NIH intramural community.

The reports for two of the components of the immediate Office of the Scientific Director follow.

Information Office

The IRP Information Office carries out all internal and external communications and information activities related to the NIA's intramural program. Many publics are served by this office including local, regional, national, and international scientists; electronic and print media; educational institutions; constituent and voluntary agencies; other State or Federal agencies; the public-at-large; and, the internal NIA staff both in Baltimore and Bethesda.

A major effort of the IO during the past year has been the planning, coordination and implementation of a two-year celebration of the BLSA's 30 Anniversary. The IO's Communication Officer chairs the planning committee; coordinates development of special displays for the participants and staff; collects, edits and packages a special 30th Anniversary information packet; supervises preparation of a new popular publication on the Study; helped plan several TV productions featuring the BLSA; and is coordinating the preparation of an orientation videotape for participants, staff and the public.

A special tour and demonstrations were arranged for 40 persons attending the 1987 Gerontological Society of America (GSA) annual meeting in Washington, and the same was done for 22 students and teachers attending the annual 1988 Maryland Junior Science and Humanities Symposium of the Maryland Academy of Sciences. Overall, the office conducted 34 tours and handled 12 speaking engagements this year, addressing over 700 individuals. Additionally, special tours were arranged for Congressman Edward Roybal, Paul Glenn of the Glenn Foundation, and four candidates for the NIA Scientific Director position.

In support of gerontological organizations, the Communications Officer edits the Maryland Gerontological Society's newsletter, edited the 1987 MGA conference proceedings, assisted with the GSA's 1987 annual meeting press room operations, and made arrangements for slides to be taken at the Center in connection with the special opening presentation of the GSA annual meeting in San Francisco November 1988. Plan to assist with 1988 GSA annual meeting media/press room.

In efforts related to employee education and welfare, the Communications Officer invited NIH Information Director, Anne Thomas, to address the Baltimore Executive Board (FEB) Public Affairs Council on, "Science, Media and the Public: The Panic About AIDS," held at the Center in June; prepared publicity for the NIH Handicapped Employees Committee workshop, "AIDS in the Workplace;" prepared programs and publicity for several handicap awareness events sponsored by the FEB Handicap Committee; chaired two Red Cross Blood Drives; coordinated or assisted with two employee awards programs; publicized seminars, speakers, educational programs or films via monthly GERON-NEWS, MGA NEWSLETTER, flyers, bulletin boards, publicity in other hospital or agency publications. In role of NIH Recreation and Welfare representative, supplied financial support for employee events such as awards programs, CFC and U. S. Bond Drive kickoffs.

A number of contracts providing building services were administered, such as those for housekeeping, security, building maintenance (heating/air conditioning/ventilation), utilities, waste disposal (general and radioactive), and radiation control.

This year, the GRC property representative conducted an annual inventory for 10 custodial areas. Also, documentation was prepared and processed for the surplus of personal property, receipt and decal of new equipment, and the coordination and physical moving of equipment/furniture within the facility.

The AO continues to monitor FTE usage and prepare reports for use by the Scientific Director and the Institute budget office. These reports help plan staffing and recruitment actions. The Administrative Officer also reviews personnel action requests before submission to the Scientific Director and, following approval initiates the actions.

The review, approval and processing of all travel documents (travel orders/travel vouchers/348s continued to be handled by this office. This past year, a new travel report was initiated enabling instantaneous, up-to-date accounting of IRP travel expenditures.

The office assisted in organizing several in-house training courses for specific groups of employees, in addition to preparing, approving, processing and following up on training completion.

The Administrative Office also carried out a wide range of responsibilities such as coordinating utility shut-downs; initiating renovation requests for specialty laboratories or areas, and for structural repairs; referring specific requests for building maintenance, i.e., lights, plumbing or temperature problems. The AO also handled accident/injury forms and information; prepared an in-house telephone directory; provided servicing of copy equipment; prepared security system building I.D. badges and entered into a security data system; issued parking permits; and, handled scheduling for two main conference rooms.

The office established an extensive liaison network with various Francis Scott Key Medical Center staff concerning on-going contracts and campus development which will directly affect the Gerontology Research Center; with the Baltimore Federal Executive Board; and, with contractor personnel servicing the Center. Close liaison is continually maintained with the NIH areas such as Disbursing Services, Travel Audit and Claims, Accounts Payable, and Contracts.

The Procurement/Receiving Unit processed 1,353 purchase orders, 2,843 Record of Calls, 645 Stock Requisitions, and 168 On-line Market Requisitions during the period August 1987 through July 1988.

Twice a year, the Procurement Office is audited. This year the Director of Delegated Procurement commended the efforts of this office in complying with the principles of the FAR, HHSAR, NIH manual issuances and the Delegated Procurement Program.

In the very near future, the IRP administrative services staff will review the latest requirements for quantity ordering through the NIH catalog. It is hoped that an in-house plan can be developed for such quantity ordering that will aid all IRP components in terms of storage and cost of supplies. Also, increased automation of some on-going administrative activities is being considered.

In summary, this year the Office of the Scientific Director has successfully aided in the overall operation of the Intramural Research Program, despite several key staff retirements, budget and travel constraints, and the HHS-wide personnel ceiling freezes. The OSD's chief secretary ran the most successful CFC campaign ever for the IRP. Several members of the OSD have won performance or other achievement awards, served on key IRP, NIH, or PHS committees, and have taken advanced training in such areas as counseling, travel, time and attendance, employment of the disabled individual, or AIDS in the workplace.

Annual Report Of The Research Resources Branch
National Institute On Aging

Technical Development Section

Two disk drives and additional memory were added to the central computer system this year. Major system software changes were accomplished that now provide a homogeneous cluster, with shadowing of the system and user's disc drives. Twenty-four served terminal ports were added this year, which allow easy access to either CPU. Training was received on a major revision to the VMS operating system which, among many other things, will allow small and inexpensive VAX CPU's to be added to our cluster. Hopefully, we can use this mechanism to off-load jobs and free up badly needed central resources.

Our in-house graphics software system was expanded to accommodate PostScript laser printers, HP pen plotters, and to interface with MacIntosh's - running very powerful illustration software. A server has been ordered to connect the central system network to the MacIntosh network, recently developed in the Photography and Arts Unit. PostScript printers have been ordered for general use in the machine room, and a general purpose typesetting program has been developed to use with them.

The development of general-purpose cards for IBM micro-computers has allowed us to begin replacing obsolete microprocessor-based equipment throughout the GRC. Currently, in various stages of development are replacements for equipment used in vigilance testing in the LPC, reaction-time testing in the BLSA, and free-recall testing, also in the LPC.

A major expansion of the VAX-controlled monkey system in the LBS is underway. It involves the addition of a dog lab, and essentially duplicating the system software.

The TDS is also involved in the development of a VAX-based, extremely high speed, data acquisition system for the LCS. For the same group, major effort was expended in the development of a program to graphically display selected elements of their large on-line data base, relating instantaneous intra-cellular free calcium cell links and transmembrane current.

Photography and Arts Unit

In addition to the normal production of negatives, slides, prints, and poster materials, the computer graphics system was expanded to include the development of new software for use in the Unit. This new software enables the Unit to produce graphs which closely match almost any type of variation presented to the Unit. Plans are being made to make this software available to any VAX user with the proper hardware. In addition, new hardware has been ordered for the VAX machine room, for use by anyone in the building.

An increased demand for service this past year was matched by an increased capacity from the computer graphics system. A considerable amount of time was saved, not only because some of the work was done by others outside the Unit, but also because the time expended on the computer is far less than the time needed for conventional processes.

A MacIntosh system was added to the Unit this year. This system will help the Unit continue to add to computer graphic's capability.

Library Unit

This year our major effort has been to implement several automated systems in our library operations. An IBM microcomputer, PS 2/Model 30, has been added and another machine is currently on order. They serve, or will serve, the following functions:

- Online Bibliographic Searching:
The librarian utilizes telecommunication software to conduct online literature searches and to download the retrieved reference onto floppy disks. Using bibliographic or word-processing software, scientists are able to transfer the retrieved data directly to their own computer reference files. This cuts down the online connecting time, and helps scientists build their own reference data base.
- Automated Serial Management Data Base REMO:
Preparation of serial holding data has been completed. The final stage of building the REMO data base is nearly complete. We are making the successful transition from manual to computerized serial record keeping.
- End-User Searching of Index Medicus on Compact Med Base:
A compact disk product of Index Medicus, Compact Med Base has been installed successfully. We are offering training and demonstration sessions, to enable the Center's staff to do their own searching on the Index Medicus.

A special project of compiling and printing an updated journal holdings book has been completed. This book also includes holdings information for the two other libraries on the FSKMC campus.

The following achievements were successfully accomplished in FY '88:

- The librarian performed 225 computerized searches on MEDLINE, BIOSIS, CA Search, PsycINFO, and Excerpta Medica data bases, through vendors of NLM, BRS, and DIALOG.
- The Center purchased 385 books this year. Out of this, 244 books have been added to the library's collection and 141 books were sent to the laboratories. For the library books, the total cost is approximately \$15,000.00. The library produces listings of these new book additions 12 times a year. These listings are published in the GERON-NEWS.
- 850 inter-library loan requests were made to serve the information needs of the intramural scientists. We also filled 150 requests for other libraries.
- 1,874 volumes of journals have been bound for the year. This figure is more than twice the number of volumes bound in FY '87.
- About 400 books, including permanent loans, were checked out from the library.

- Approximately 250,000 copies were made on the library's copy machine. A new copier has been in use since July.
- 82 journal titles have been deleted. These titles were recommended for deletion by former Library Committee members and the librarian, based on the criteria of frequency of usage, updatedness of holdings, and the scope of the Center's research interests.

Animal Resources Section

The following achievements were successfully accomplished in FY '88:

- Maintained accreditation with the American Association for Accreditation of Laboratory Animal Care (AAALAC) for the 11th consecutive year.
- Maintained institutional membership with the American Association of Laboratory Animal Science (AALAS), as well as with its local National Capital Area Branch (NCAB).
- A total of 5,012 mice and rats, of varying ages, were issued from the aging colonies.
- The staff spent 139.5 hours supporting 47 aseptic surgical procedures.
- In addition to our stock animals, approximately 6,237 mice, 2,184 rats, 367 rabbits, 10 primates, 6 dogs, and 2 pigs were received and housed by the ARS.
- The ARS was able to supply approximately 120 rats and 102 mice to other scientific institutions throughout the country.
- The ARS staff authored/co-authored two publications.
- The ARS collaborated in the cage design for tethering primates and dogs.

Instrument, Design, and Fabrication Section

In the past year, along with many 30 minute to 2 hour construction and repair jobs, the section designed, fabricated, and installed equipment. This equipment includes a large, anti-magnetic radiation cage for the MRI, a special multi-sample cartridge separation rack, a fiber optic microscopic fluorescence image analyzer, a tilting bed, heliarc welding of special gas cylinder racks, and other long-term projects.

ANNUAL REPORT OF THE LONGITUDINAL STUDIES BRANCH

NATIONAL INSTITUTE ON AGING

The FY1988 Annual Report of the Longitudinal Studies Branch (LSB) is different in format and organization from its sister laboratories because of the special nature of its activities. The function of the LSB was dictated by a staff-perceived need for an overall plan and set of operating principles for a major multidisciplinary longitudinal study, the Baltimore Longitudinal Study of Aging (BLSA). Lack of central planning during the 30 year history of the Study has resulted in a number of projects continuing with little or no direct scientific supervision; and many of these were left as a legacy to the LSB when it was created in FY1986. For each of these projects, aggressive efforts were initiated to accomplish the following: bring the quality of the activity up to acceptable scientific standards; get the longitudinal story of the research told; reevaluate the scientific value of the project; and plan and implement new directions for the research in question. Examples of such projects include clinical evaluation, hearing, pulmonary function, reaction time and vision.

Some research activities in the LSB are designed to promote the work of many investigators who use the BLSA. Examples include studies on the morbidity and mortality of participants, diagnoses and medications used, and demographic information. In addition new applications of statistics and methodology for longitudinal studies are being developed which benefit many investigators.

In tandem with its research activities, the LSB manages and operates the BLSA. When the Branch was created in FY1986, the duties of all personnel except for the Chief and the mathematical statistician were assigned to this activity, and today the duties of all LSB staff include both a research and service component. Staff activities range from recruitment of new participants and management of the activities of the Study to obtaining and analyzing information about deceased BLSA participants. Goals for the size and composition of the sample consistent with BLSA objectives have been established, and all ongoing recruitment and retention activities are organized around those objectives. A rationale and process for obtaining and analyzing information from inactive participants was developed and will be implemented in FY 1989. Two systems for determining the underlying cause of death of deceased participants have been developed and put in place, and the uncertainty of information about participants who die has been dramatically reduced. An autopsy program has been established and all participants are invited to allow their bodies to be autopsied following their death.

During the year a major effort has been initiated to review the overall use and quality of the data collected in the BLSA. Senior investigators in the BLSA have been asked to identify those data sets which they believe will be of greatest use to future investigators, and the actual use of the same data is being reviewed by LSB staff. The purpose of these activities are to maximize the utilization of all data being collected and to identify ways of bringing new resources and talent to bear on the unmet needs of the BLSA.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00015-30 LSB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

The Baltimore Longitudinal Study of Human Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

J. L. Fozard	Chief.	LSB, NIA
	and Associate Scientific Director	BLSA, OSD, NIA
L. J. Brant	Mathematical Statistician	LSB, NIA
E. J. Metter	Medical Officer	LSB, NIA
N. W. Shock	Scientist Emeritus	NIA
C. Morrell	IPA, Loyola College, Baltimore, Statistics	
M. Tockman	IPA, School of Hygiene	JHU

Other Investigators: See next page

COOPERATING UNITS (if any)

Francis Scott Key Medical Center (FSKMC); National Institute of Dental Research (NIDR); Johns Hopkins University (JHU)

LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

SECTION

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

14.95

PROFESSIONAL:

5.0

OTHER:

9.95

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The Baltimore Longitudinal Study of Aging (BLSA), the NIA's major research program on human on human aging, has been conducted at the Gerontology Research Center since 1958. The overall scientific goals of the BLSA are:

To identify differences among individuals of different ages and changes that occur in the serial observations of these individuals with the passage of time; to determine the relative contribution of aging, disease processes, cohort effects and secular effects in producing observed differences and changes; and to establish the degree of interrelation and/or interaction among these factors.

To expand scientific understanding about predictors and risk factors for specific diseases and for other end points related to successes and failures of adaptation to aging processes.

Scientists working with BLSA are assigned to 11 sections of 7 laboratories in addition to the LSB. LSB staff administer and manage the BLSA as well as conduct research with it.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00241-06 LSB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Development of Statistical Methodology for the Analysis of BLSA Data

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

Larry J. Brant

Mathematical Statistician

CPB, NIA

COOPERATING UNITS (If any)

LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

SECTION

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

This project has been incorporated in Baltimore Longitudinal Study of Aging (BLSA) Project #Z01 AG 00015-30 LSB.

ANNUAL REPORT OF THE LABORATORY OF BEHAVIORAL SCIENCES

NATIONAL INSTITUTE ON AGING

Significant Administrative Events

The major administrative event in FY88 is the completion of the Geriatric Continence Research Project. This project is a three-year study of the cost/effectiveness of various behavioral treatments of incontinence in long-term care patients. The project was jointly funded by NIA and the Health Care Financing Administration, and was based in a 15 bed unit in the Mason F. Lord, Long-term Care Building of the Francis Scott Key Medical Center. The unit was officially closed in August, 1988; however, follow-up studies will not be completed until November, 1988.

Scientific Accomplishments

Behavioral Medicine Section (BMS)

There are four major program areas in this section; and each area has a number of clinical projects.

1. Last year we closed our outpatient continence research unit. However, data analyses of some of the studies completed during the previous year are still under way or have been submitted for publication within the past year. Two studies are now in press: (a) One has shown that it was possible to effectively treat incontinence in a group of 20 men with persistent post-prostatectomy incontinence. In particular, following 1-5 biofeedback sessions, the prevalence of urge incontinent episodes was reduced an average of 81% and stress incontinent episodes were reduced an average of 78%. Total incontinence (continual leakage) was reduced by 17%. Thus, these findings show that biofeedback training is an effective intervention for episodic stress or urge incontinence following prostatectomy; however, it has only limited usefulness in the control of continual leakage. (b) Another study which is now in press showed that an internist/geriatrician and a nurse practitioner, operating in a traditional office practice setting can effectively treat elderly, non-demented, ambulatory, incontinent patients. In a series of 27 outpatients with symptoms of stress, urge or mixed incontinence, it was possible to effectively reduce incontinent episodes by about 80% using biofeedback and/or habit training techniques. Thus, this study shows that behavioral treatments of urinary incontinence can be extremely cost/effective since they can be implemented successfully in an office setting without the need for expensive urodynamic evaluations. The final report from this program for this year is an epidemiological study of healthy, perimenopausal women conducted in collaboration with colleagues at the University of Pittsburgh School of Medicine. In a randomly selected cohort of community-dwelling women aged 43 to 51 years, we found that 52% reported at least one episode of involuntary urine loss in their lifetimes, 34% reported loss at least once/month, 20% reported weekly accidents and 6% were incontinent on a daily basis. It is of particular interest that only 24% of these women ever sought help from a health professional to manage her incontinence.

In addition to these outpatient studies, we also have operated an intensive study of behavioral treatment of urinary and/or fecal incontinence in the long-term care setting. Although this study is still in progress (data collection should be completed by November, 1988), results to date indicate that it is possible to treat even severely demented patients in a long-term care setting, and to maintain these clinical gains for at least three months post-treatment. Critical to the success of the maintained improvement is the implementation of a staff management program which can be carried out by indigenous nursing staff. Results to date show that our program resulted in an 8% reduction in urinary incontinent episodes and a 7% reduction in fecal incontinent episodes, 3 months after discharge from the program. Since this represents a reduction of about one episode/patient/day, and since the cost of a single incontinent episode has been estimated to be about \$1.60, and since there are about 800,000, incontinent, long-term care patients in the United States, this outcome reflects a potentially considerable cost savings. An independent study, directed by the Health Care Financing Administration and specifically designed to assess cost/effectiveness of our program, has recently been implemented. Results from this study should yield important findings on the value of behavioral treatment of incontinence in the long-term care setting.

In addition to this treatment program, we have recently completed a survey of documentation of incontinence in a long-term care setting that we had studied several years earlier. The findings of this recently completed survey reveal that there has been a significant improvement in nursing documentation of incontinence. It seems likely that this improvement in documentation reflects both a heightened awareness of incontinence as a clinical condition, and a deeper recognition that incontinence is a potentially treatable condition.

2. Last year we reported that a Behavioral Stepped-Care treatment program was cost/effective in the management of mild to moderate hypertension. A study describing those findings in greater detail is now in press. In addition, we have completed a pilot study to evaluate the effectiveness of the Stepped-Care program in the control of isolated systolic hypertension (ISH) in the elderly. We studied 15 patients who met traditional criteria for ISH. Our findings revealed that by the end of a six-month program of behavioral treatment featuring patient-administered systolic pressure biofeedback and relaxation, patient-determined blood pressures fell significantly (13/8 mm Hg), and professionally-determined blood pressures also fell significantly (8/6 mm Hg). During the next year we will try to implement a cooperative study to evaluate the Behavioral Stepped-Care treatment further.

3. An extensive and comprehensive study of age differences in cardiopulmonary performance during a standardized abdominal breathing task was completed this year. The study included 120 men and women ranging in age from 21 to 89 years. Furthermore, the group was selected to have equal representation of smokers and nonsmokers as well as subjects who regularly exercised and those who did not. Among the many interesting findings in this study, the following are especially noteworthy: (a) Fatigue (inspiratory time/total breath time) increases progressively with age; (b) In general, there

were age-related declines in gas exchange performance; however, factors such as sex, exercise and smoking history also contributed; (c) Various cardiovascular indices such as left ventricular work, total peripheral resistance and blood pressure increased with age; (d) There were no age differences in lung volume although most gerontological studies have noted such changes. Possibly, matching the age groups by sex, exercise and smoking history reduced such differences. In addition to their intrinsic value, these data should provide a normative basis for a variety of future studies. Since this cohort has been carefully selected on a number of variables, it should be possible to use the data base to provide a set of norms for future studies -- e.g., with patient groups.

4. As noted below, we have been conducting a major research program of study on diurnal hemodynamic patterns in animals. The main findings from that program have been that cardiac output falls throughout the night, and that peripheral resistance rises so that the lowest level of output and highest level of resistance occurs daily between 5 AM and 7 AM. Further evidence suggested that this hemodynamic pattern was mediated, in part, by a fall in plasma volume. Since a change in plasma volume could be associated with changes in concentration of plasma proteins, and in the concentration of various substances such as drugs which are bound to proteins, we implemented studies of diurnal patterns of drug concentration in patients. Although these studies have only recently begun, the findings suggest that there may be diurnal increases in the concentration of some drugs. Current plans are to complete the existing studies and to implement other research projects, focusing in particular on drugs that are taken on a daily basis to manage chronic conditions often seen in older persons.

Behavioral Physiology Section (BPS)

The scientific principle underlying all research programs in LBS is that any neurally mediated response is a behavior. Thus, any attempt to understand physiological function of neurally mediated responses must identify behavioral as well as physiological mechanisms. Research in the Behavioral Medicine Section applies this principle to the assessment and treatment of patients; research in this section is designed to identify and characterize the relevant physiological and behavioral mechanisms.

1. Exercise behavior has always been a subject of considerable interest to physiologists. This interest derives from a number of reasons: exercise ability is an important aspect of natural selection; exercise involves the integration of multiple response systems; and exercise is a clinically important behavior since it is highly correlated with cardiovascular and pulmonary function. Thus, LBS has had a long-standing interest in exercise both in BMS and BPS. Our studies in BPS have focussed on the role of the central nervous system in the integration of cardiovascular, pulmonary and somatomotor behaviors. We have trained monkeys to exercise, to slow their heart rates and to attenuate the tachycardia of exercise. Current research is directed at identifying the mechanisms of cardiovascular control during exercise: In particular, we are attempting to learn whether the central

neural control of the circulation during exercise is mediated by somatomotor behaviors, or whether the circulatory responses can be modified independently of the somatomotor responses. Ongoing studies with autonomic blocking drugs indicate that a animal that has been trained to slow its heart while exercising can continue to do so even when one or another branch of the autonomic nervous system is blocked; however, in order to accomplish this behavior, the animal must make a variety of compensatory adjustments depending upon the available neural pathways. Thus, our findings indicate that: (a) the central control of circulatory behavior can be disassociated from the central control of somatomotor behavior; (b) animals that are trained to regulate heart rate during exercise are more efficient when they are controlling heart rate than they are when they exercise freely at the same task, i.e., they accomplish the same somatomotor performance while emitting less left ventricular work; (c) the animals learn to produce the required target behavior, not to respond via a specific neuromotor pathway. Thus, autonomic blocking agents do not abolish the ability of the animal to perform, but they do cause changes in the mechanism of the expression of the learned behavior.

2. There is a great deal of clinical evidence that major circulatory events such as myocardial infarctions, strokes or incidence of sudden death are not randomly distributed throughout the day but are more likely to occur at certain times of the day. Since this is so, it seems likely that there must be a physiological basis for this. Thus, LBS has been studying the hemodynamic changes that occur in the circulation throughout the night and morning hours. Earlier we found that in monkeys, cardiac output fell throughout the night and that peripheral resistance rose, presumably to maintain blood pressure homeostasis in the face of reduced output. Since the fall in output must reflect a fall in venous return, we carried out studies during the past year to determine whether the decline in venous return reflected a redistribution of the blood volume -- e.g., to the venous beds, or a actual reduction in plasma volume. Studies done this year with sympathetic nervous blocking agents have shown that redistribution of blood volume cannot be the primary mechanism for these hemodynamic changes since drugs that block the ability of the nervous system to redistribute blood volume not only do not abolish these hemodynamic changes, they exacerbate them. Thus, these findings suggest strongly that there are significant changes in blood volume throughout the night, and that these changes may have clinical significance (see the BMS report above).

Sympathetic blocking agents are used to treat a variety of cardiovascular disorders. However, as noted above, these produce diurnal changes in the circulation which may be harmful. In order to illustrate the different effects which various drugs could have on hemodynamic performance, we compared a widely used antihypertensive drug, the cardiac-specific beta-blocker, atenolol, with another antihypertensive drug, the calcium entry blocker, verapamil. We found that these two drugs lowered blood pressure about equally, but that atenolol also exacerbated the rise in peripheral resistance whereas verapamil attenuated this effect. Given that one of the clinical characteristics of hypertension is increased peripheral resistance, it

would seem that a drug which raises resistance further is not clinically helpful, and that one that lowers resistance would be more desirable. Furthermore, our findings suggest another important consideration in the selection of cardiovascular medication; namely, the action of the drug during the nighttime.

Our studies have shown significant diurnal, hemodynamic patterns in monkeys. Other studies have reported similar patterns in rodents, and less clearly in man, in part because of technical, measurement problems. In order to determine the ubiquity of these hemodynamic patterns, we have established a dog laboratory where it will be possible to get comparable hemodynamic data. The dog is an important model for study because it is a carnivore, and this order may be uniquely different from other mammals which are herbivores or omnivores; and the dog also is an important model for study since so much cardiovascular research is based on findings with this species.

3. One of the most common clinical problems characteristic of older people is that they show indications of a decline in thermoregulatory ability. In particular, they are at greater risk for hypothermia in cold weather conditions, and they report feeling cold in settings where most younger subjects report being comfortable. LBS has maintained a continuing program of study of the mechanisms underlying thermoregulation. We have shown that adult, but not old, C57/BL mice show habituation to repeated cold exposure; i.e., their body temperatures does not fall as much during subsequent, regularly scheduled tests. Current research is showing that the adult animals learn to increase metabolic heat production during repeated exposure to a cold environment, but old animals do not show this skill. Additional studies of the effect of varying the interval between the time the animal is experimentally prepared to be introduced to the cold environment, and the time of actual introduction have shown that adult animals are able to discriminate between experimental restraint and actual cold stress while old animals did not show this behavior; i.e., the adult animals emitted greater heat production during the restraint condition and the cold condition when they were given an hour of prior restraint, but the old animals failed to acquire this discrimination.

Finally, as noted above LBS is systematically studying the diurnal patterns of cardiovascular behavior. Since the circulation is a major system in thermoregulation, we also are looking at diurnal variations in age differences in thermoregulation. In particular, we are exploring the effect of time of day on the age differences in heat production to learn if this could be a factor in habituation of cold tolerance. It should be recognized here that mice are nocturnal animals; thus, their typical days end in the morning and begin in the evening which is the opposite of that for normal man. Our findings indicate that among adult animals the rate of decline of colonic temperature during cold exposure is greater in the afternoon than it is in the morning; however, this index of cold tolerance is not paralleled by changes in metabolic heat production which does not vary as a function of time of day. Old animals do not show a time of day effect either for cold tolerance or for metabolic heat production.

These findings suggest that the time of day effect is a reflection of shifts in heat conservation whereas the age differences reflect differences in heat production.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00063-20 LBS

PERIOD COVERED

October 1, 1987 to September 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Learned Modification of Visceral Functions in Animals

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Bernard T. Engel, Ph.D.	Chief, Laboratory of Behavioral Sciences	LBS, NIA
David E. Anderson, Ph.D.	Chief, Behavioral Medicine Section	LBS, NIA
Mark I. Talan, M.D., Ph.D.	Medical Officer	LBS, NIA
Harold Tatelman, Ph.D.	IRTA Fellow	LBS, NIA

COOPERATING UNITS (if any)

Laboratory of Cellular and Molecular Biology, NIA; University of California, San Diego Medical School

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Behavioral Medicine Section

INSTITUTE AND LOCATION

NIA, NIH, Gerontology Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:

8.7

PROFESSIONAL:

3.1

OTHER:

5.6

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

The purpose of this project is to investigate the role of the central nervous system in behavior. In some experiments we are studying the extent to which the cardiovascular system can be modified by instrumental conditioning. In other experiments, we are examining age-related changes in thermoregulation. In other experiments, we are examining diurnal patterns of hemodynamic performance.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00067-20 LBS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Learned Modification of Visceral Function in Man

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

Bernard T. Engel, Ph.D.	Chief, Laboratory of Behavioral Sciences	LBS, NIA
David E. Anderson, Ph.D.	Chief, Behavioral Medicine Section	LBS, NIA
Kathleen A. McCormick, R.N., Ph.D.	Nurse-Director	LBS, NIA
Linda Moody, Ph.D.	IPA Fellow	LBS, NIA

COOPERATING UNITS (if any)

Dr. K.L. Burgio, University of Pittsburgh School of Medicine; Francis Scott Key Medical Center; The Johns Hopkins University School of Medicine; Longitudinal Studies Branch, NIA

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Behavioral Medicine Section

INSTITUTE AND LOCATION

NIA, NIH, Gerontology Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:

6.7

PROFESSIONAL:

2.3

OTHER:

4.2

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is concerned with the application of behavioral methods and principles to clinical medicine. Subjects are patients selected from various medical clinics, or normal subjects who are studied to evaluate potential clinical methods. The main focus of this project is on clinical problems especially relevant to middle-aged or elderly persons.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00071-02 LBS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Isolated Systolic Hypertension

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

Bernard T. Engel, Ph.D. Chief, Laboratory of Behavioral Sciences LBS, NIA

COOPERATING UNITS (if any)

Francis Scott Key Medical Center

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Behavioral Medicine

INSTITUTE AND LOCATION

NIA, NIH, GRC, Baltimore, MD 21224

TOTAL MAN-YEARS:

.2

PROFESSIONAL:

.1

OTHER:

.1

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Isolated systolic hypertension is a common problem among elderly persons. This project is designed as a pilot study to estimate the clinical effectiveness of a behavioral stepped-care program to lower systolic pressure in these patients.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00072-02 LBS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Behavioral Assessment and Treatment of Incontinence in Nursing Home Residents

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

Bernard T. Engel, Ph.D. Chief, Laboratory of Behavioral Sciences LBS, NIA
Kathleen A. McCormick, R.N. Ph.D. Nurse-Director LBS, NIA

COOPERATING UNITS (if any)

Dr. L.D. Burgio, University of Pittsburgh School of Medicine; Francis Scott Key Medical Center; Health Care Financing Administration; Office of the Surgeon General of the United States

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Behavioral Medicine

INSTITUTE AND LOCATION

NIA, NIH, Gerontology Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:

2.1

PROFESSIONAL:

1.0

OTHER:

1.1

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Incontinence is a major reason for institutionalizing elderly persons, and is widespread in nursing homes. This project is designed to evaluate behavioral intervention techniques for the treatment of these patients.

Annual Report of the Laboratory of Biological Chemistry

National Institute on Aging

The Laboratory of Biological Chemistry conducts fundamental and original research on the molecular basis of life processes important to the understanding of aging and the pathophysiology of age-associated disorders. The Laboratory's scientists investigate the mechanisms regulating intracellular and extracellular environments; metabolism; structural integrity; cell division, growth and differentiation; physiological functions; and vitality. Particular attention is paid to the role of hormones and growth and differentiation factors, and signal transduction mechanisms eliciting cellular responses.

The Regulatory Mechanisms Section examines how mineral metabolism is regulated at the cellular, suocellular and molecular biology levels and studies the mechanisms by which these systems become altered in age-related osteopenia and osteoporosis. Cell culture lines of bone, kidney and intestine are developed as models and exploited. In addition, various cell and membrane preparations are used to investigate the control of intracellular pH, calcium and ion flux, factors essential for cell division, growth, differentiation and metabolism. Signal transduction mechanisms in mediating cell responses are investigated as well as the changes that occur in these systems during the aging process.

The Membrane Biology Section seeks to determine the chemical nature and sequence of intermediate reactions controlling the movement of cations through ionic channels and pumps. The behavior of these systems with respect to energy utilization and energy transduction, ion selectivity, gating mechanisms, and sensitivity to hormones and pharmacological agents are characterized. Studies concern how the affinity, capacity and selectivity of ion translocation mechanisms are affected by aging.

1. Effect of age on vitamin D receptor binding to rat DNA. The age associated decline in Ca^{++} absorption from the intestine was correlated both with lower $1,25(\text{OH})_2\text{D}_3$ levels and lower intestinal Vit D receptors (VDR). Intestinal VDR from 24 month rats when compared to 6 month rats exhoited a different aggregation pattern after sucrose gradient ultracentrifugation. Intestinal VDR from both 6 and 24 month rats preferentially bound to liver DNA from 6 month rats compared to DNA from 24 month rats. VDR from the young rats bound to DNA with higher affinity than VDR from old rats.

2. Fluorescent microscopic imaging of cells. Rapid digitization of fluorescent images of cells loaded with Ca^{2+} and pH indicating dyes has been achieved with lymphocytes, fibroblasts, and parathyroid cells, and bone cells. In collaopora-tion with Dr. Al Nordin, Laboratory of Clinical Physiology, Clinical Immunology

Section, discrimination between T₂ and T₄ cells in a suspension of resting lymphocytes was achieved using fluorescent dyes linked to antibodies. In collaboration with Dr. Norndra Singh, Laboratory of Molecular Genetics, digitization of fluorescent images of electrophoretic patterns of large DNA fragments from human lymphocytes has been done. Software appropriate to compare qualitatively and quantitatively patterns in different cells has been obtained and is being used for this and analogous studies.

3. Mechanism for the decrease renal ammonia excretion after an acid load in old rats. Last year we reported that ammoniagenesis in nephron segments was increased by an acid load in both young (6 mo) and old (24 mo) rats when compared to young rats, ammonion excretion in old rats was significantly lower. We examined the serum glutamine concentrations in each age group. Old control rats have lower serum glutamine and old acidotic rats have higher glutamine levels than young rats. Since the main source of serum glutamine was muscles, we speculated that the reduced glutamine concentration in old control rats was related to their smaller muscle mass. The increased serum glutamine levels observed in old acidotic rats was likely due to the combination of increased synthesis of glutamine by the muscles and decreased utilization by the kidneys. Metabolic acidosis increased the apparent affinity of the S1 segment for glutamine in young rats, but caused no change in old rats. When the serum glutamine levels were used to calculate ammoniagenesis in young and old acidotic rats, we found no difference between the two groups. We therefore conclude that the deficit in ammonia excretion in 24 month acidotic rats compared to 6 month rats is related to 1) the age-associated reduction in the functional renal mass and 2) the age-associated differences in serum glutamine and apparent affinity of the S1 segment for glutamine that negate each other.

4. Age-associated changes in gene expression of the α subunit of GTP-binding proteins in rat renal cells. We have reported that PTH dependent change in renal Na⁺/Ca²⁺ exchange activity declined in senescent rats. This age-associated defect may in part be attributed to a lower response of renal adenylate cyclase to PTH. We also reported that levels of GTP-binding proteins which couple hormone receptor to the catalytic unit of adenylate cyclase decrease in senescent rats. To assess whether this shortcoming is at the molecular level, we prepared RNA samples from adult (6 mo) and old (24 mo) rats by guanidinium/CsCl method and measured the levels of α_s and α_i (subunits for Gs and Gi), actin, and poly(A)⁺ mRNA. Purity and recoveries of RNA and mRNA were similar for both age groups. RNA samples were applied on the dot blot and probed with cDNA for α_s , α_i , actin and poly(A)⁺ RNA.

	mRNA				Relative Abundance of mRNA		
	poly(A) ⁺	α_s	α_i	Actin	α_s	α	Actin
6mo	0.28±0.03	0.31±0.02	0.22±0.02	0.65±0.04	1.23±0.09	0.84±0.04	2.56±0.13
24mo	0.38±0.04	0.28±0.02	0.38±0.03	0.88±0.04	83±0.06	1.08±0.06	2.77±0.21
	p<0.05	N.S.	p<0.01	p<0.01	p<0.01	p.<0.01	N.S.

Our findings suggest that (1) total mRNA and mRNA of α i and actin increase in old rat whereas α s does not change with age, (2) the relative abundance of α s decreases and α i increases in the old rat with no apparent change in actin.

5. Relationship of PTH responsiveness in isolated nephron segments with age.

Renal cAMP generation in response to PTH is reduced in renal cortical cells of 24 month old rats when compared to younger 6 month old rats. This decrease could be due to a differential loss of only PTH responsive cells relative to other cell types or to a general decrease in responsiveness of all remaining cells. To address this question, we examined in isolated nephron segments adenylate cyclase activity after the addition of PTH, calcitonin, glucagon, vasopressin, or forskolin. Segments from 6 month rats and 24 month rats with "normal" BUN and serum creatinines were compared. No significant age-associated differences were found for any hormone in any segment. When PTH-stimulated (convoluted tuoule) adenylate cyclase activity was measured in accessible S1 segments from 24 month rats with variable BUN's and serum creatinines, there was no correlation between adenylate cyclase activity and BUN or creatinine. We conclude that the previously described decline in cAMP generation in renal cortical cells in response to PTH is not universal for all nephrons and is at least in part due to progressive deterioration of nephrons

6. Neurotransmitter regulation of cytosolic Ca^{2+} in bone cells (UMR-106).

ATP was found to increase cytosolic Ca^{2+} transiently in UMR-106 cells 2-3 fold more than PTH. Norepinephrine and vasoactive intestinal polypeptide also elicited transients that were smaller than with PTH. ATP stimulation persisted in the presence of EGTA and was associated with increased labeling of IP_3 , while NE and VIP stimulation were partially dependent upon extracellular Ca^{2+} . The order of potency for ATP and analogs was $\text{ATP} = \text{ADP} > \alpha, \beta\text{-methylene ATP} > \text{AMP} = \text{adenosine}$, indicating mediation through a P2-purinergeric receptor.

The changes in Ca^{2+} produced by ATP and NE were multiphasic, consisting of a rapid rise, followed by a rapid fall to sub-basal values, then followed by a slow, sustained rise to a level above the initial, basal value. The late, sustained phase was dependent upon extracellular Ca^{2+} . 2-Methylthio-ATP produced an even more complex sequence of changes: a rapid rise and fall, followed by a second, slower, smaller rise and fall, followed by a slow rise to a sustained level above basal. Both the transient second phase and sustained increase were dependent on extracellular Ca^{2+} .

7. Age-associated changes in hormonal regulation of cytosolic Ca^{2+} in proximal tubules of female rats.

Hormonal regulation of cytosolic Ca^{2+} in response to PTH was reduced significantly in 24 mo female rats compared to 6 mo rats, from a 50% increase to approximately a 30% increase. In comparison, norepinephrine increased cytosolic Ca^{2+} 120% in tubules from 6 mo females and 100% in tubules from 24 mo rats. Mean BUN for 6 and 24 mo females was 23 and 35, respectively. This increase in BUN is somewhat less than that was previously described for 24 mo male rats, and no clear relationship exists at present between BUN value and PTH responsiveness as observed with male rats.

8. Efficiency of energy coupling declines with age in cardiac muscle sarcoplasmic reticulum. Although active Ca^{2+} transport in cardiac in sarcoplasmic reticulum (SR) requires ATP as an energy source, the mechanism involved in the conversion of chemical energy to osmotic work has not been established. This issue has acquired special significance this year because of recent findings demonstrating that the age-dependent decline in Ca^{2+} transport in rat cardiac SR is not accompanied by a stoichiometric decrease in CaATPase activity. Previous attempts to measure Ca^{2+} -dependent phosphate production linked to active Ca^{2+} transport were hampered by an unusually high background activity arising from a Mg^{2+} -dependent ATPase present in contaminating membranes from the sarcotubular system. To overcome this difficulty, a method was devised to measure Ca^{2+} -dependent ATP hydrolysis indirectly from the steady state level and rate of decay of the obligatory phosphoenzyme intermediate generated by phosphorylation of the Ca^{2+} pump by ATP. By using rapid acid quenching to initiate formation of the phosphoenzyme and monitor its disappearance following dilution of the labelled substrate, we were able to demonstrate that turnover of the phosphoenzyme in 24-26 month old animals occurred at a rate ($12.60 \pm .89 \text{ s}^{-1}$; $n = 6$) that was not significantly different from that found in the young (6-8 mo) population ($12.08 \pm .71 \text{ s}^{-1}$; $n = 6$). In addition, the steady state levels of phosphoenzyme did not differ significantly in the two age groups ($.462 \pm .05 \text{ nmol/mg}$ in the young vs $.471 \pm .08 \text{ nmol/mg}$ in the old), confirming earlier results indicating that the density of Ca^{2+} transport sites is independent of age. Since the overall rate of ATP hydrolysis coupled to Ca^{2+} transport is equivalent to the phosphoenzyme level multiplied by its rate of decay, it is apparent that CaATPase activity does not change with age. The initial uptake of Ca^{2+} measured under similar conditions using Ca^{2+} -sensitive dyes and stopped-flow mixing was previously shown to be about 25% higher in young animals ($4.28 \pm .33 \text{ nmol/mg/sec}$) as compared to old ($2.92 \pm .31 \text{ nmol/mg/sec}$), implying that the transport ratio (Ca^{2+} transported/ATP hydrolyzed) of the Ca^{2+} pump declines with age. This could reflect an age-dependent decrease in the efficiency of chemical energy conversion or an increase in the population of unsealed membrane vesicles.

9. Diminished Ca^{2+} transport efficiency in sarcoplasmic reticulum accompanies the removal of a 53 kDa glycoprotein. The demonstration of an age-related decline in the efficiency of energy utilization in rat cardiac SR has prompted the search for an appropriate model in which to study the mechanism of energy transduction. Examination of the factors that influence the degree of energy coupling in skeletal muscle SR by Dr. Howard Kutchai at the University of Virginia has demonstrated that the loss of efficient energy coupling between ATP hydrolysis and Ca^{2+} transport is correlated with the removal of a 53 kDa membrane-bound glycoprotein by high salt extraction in the presence of cholate. Because the functional properties associated with this protein strongly implicate its involvement in energy transduction, it was important to determine

how glycoprotein removal alters the relationship between Ca^{2+} translocation and the energy-yielding CaATPase partial reactions. Evaluation of the kinetic properties of the transport reactions in glycoprotein-depleted membranes was carried out by quenched-flow analysis using membranes extracted with low salt (which retain the glycoprotein) as a control. Partial extraction of the glycoprotein had no effect on Ca^{2+} translocation associated with the initial turnover of the pump, but strongly inhibited Ca^{2+} accumulation in the steady state. In addition, phosphoenzyme formation in the presteady state was slowed compared to the control and exhibited a biphasic pattern of accumulation. No differences were found with respect to the maximum level of phosphorylation, steady ATP hydrolysis or ADP-induced dephosphorylation of the phosphorylated enzyme. These findings are consistent with uncoupling of ATP hydrolysis from Ca^{2+} transport after completion of the initial cycle of Ca^{2+} translocation and suggest that the mechanism for this change involves a defect in carrier recycling.

10. Calcium-induced Ca^{2+} release in cardiac sarcoplasmic reticulum is unaltered with age. Release of Ca^{2+} from the SR, which leads to the development of active tension in cardiac muscle, is activated by a rise in myoplasmic Ca^{2+} . This activity is retained by isolated cardiac SR vesicles and is blocked by high Mg^{2+} , which can be used as a quenching reagent in investigations of the mechanism of Ca^{2+} release. In a continuation of studies begun last year, additional work has been completed to characterize the channel-mediated Ca^{2+} translocation pathways in SR vesicles isolated from young and old rat myocardium.

Effect of Age on Ca^{2+} -Induced Ca^{2+} Release in Rat Cardiac SR

Age (mo)	Total Ca^{2+} (nmol/mg)	Fractional Amount			Efflux Rate		
		A	B (%)	C	k_a	k_b (s^{-1})	k_c
6-8	18.1 $\pm$ 1.8	11.0 $\pm$ 3.0	13.0 $\pm$ 2.0	76.1 $\pm$ 2.0	1.13 $\pm$.13	.19 $\pm$.04	.0048 $\pm$.0003
24-26	19.7 $\pm$ 1.3	9.3 $\pm$ 4.6	14.9 $\pm$ 2.0	76.8 $\pm$ 1.9	1.48 $\pm$.51	.24 $\pm$.05	.0038 $\pm$.0007
	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

At a free Ca^{2+} level of 2 μM , Ca^{2+} release from passively-loaded SR vesicles was resolved into 3 distinct phases accounting for roughly 10, 15 and 75% of total Ca^{2+} trapped in the vesicles. Analysis of the kinetics of Ca^{2+} release revealed that there were no significant age differences with respect to the rate or fractional amount of Ca^{2+} release in each phase. These results are consistent

with evidence showing that the rise in intracellular Ca^{2+} recorded in papillary muscle fibers during contraction is not age-dependent (Orchard C. H. and Lakatta, E. G. (1985) J. Gen. Physiol. 86:637-651) and exclude Ca^{2+} -induced Ca^{2+} release as a factor contributing to the decline in Ca^{2+} transport function in cardiac SR isolated from old rats.

11. Activation of the Na^+/H^+ exchanger by internal H^+ changes the functional subunit composition of the exchanger. Under the conditions promoting optimal levels of transport activity (i.e. low internal pH, high external pH and Na^+), the pattern of amiloride-sensitive Na^+ uptake by renal brush border membrane vesicles consists of a presteady state burst followed by a linear (steady state) phase of accumulation. By raising the internal pH and preventing the occupation of the internal H^+ transport and regulatory sites, we were able to limit the activity of the exchanger to single turnover. The burst rate remained the same under these conditions but the maximum burst amplitude was reduced to about half the normal level. Analysis of the kinetics of the burst phase under conditions where the exchanger was allowed to cycle continuously revealed that a minimum of 4 interacting subunits (each with a single Na^+ binding site) were necessary to explain the complex dependence of the burst amplitude on Na^+ concentration. In contrast, the $[\text{Na}^+]$ dependence of the burst phase under single turnover conditions obeyed Michaelis-Menten kinetics indicating the presence of a single Na^+ binding site. The changes in Na^+ transport that result from acidification of the intravesicular medium are inconsistent with a simple mechanism in which loading of an internal H^+ transport site allows recycling to occur. Rather, internal protons appear to recruit additional exchangers and promote their interaction by a mechanism that raises the overall level of Na^+ flux through the system. Hormones and growth factors, which are known to enhance Na^+/H^+ exchange activity, may utilize this mechanism to activate the exchanger by increasing the sensitivity of internal transport and regulatory sites to protons.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00051-08 LBC

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Regulation of Mineral Metabolism

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

Bertram Sacktor	Chief, Laboratory of Biological Chemistry	LBC	GRC	NIA
C. Tony Liang	Research Chemist	LBC	GRC	NIA
Sandra Guggino	Senior Staff Fellow (MBS)	LBC	GRC	NIA
James Kinsella	Research Physiologist	LBC	GRC	NIA
Charles Filburn	Research Chemist	LBC	GRC	NIA
Shoshi Takamoto	Visiting Fellow	LBC	GRC	NIA
Daniel Lajeunesse	Visiting Fellow	LBC	GRC	NIA
Hideo Yamada	Visiting Fellow	LBC	GRC	NIA
Rajendra Prasad	Visiting Fellow	LBC	GRC	NIA

COOPERATING UNITS (if any)

H. F. DeLuca	Dept. of Biochemistry, U. of Wisconsin, Madison, WI
M. E. Burns	Dept. of Pathology, U. of Virginia, Charlottesville, VA

LAB/BRANCH

Gerontology Research Center, Laboratory of Biological Chemistry

SECTION

Regulatory Mechanisms Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS

8.8

PROFESSIONAL:

5.6

OTHER:

3.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects	☒ (b) Human tissues	☐ (c) Neither
☐ (a1) Minors		
☐ (a2) Interviews		

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This report describes studies on the regulation of mineral metabolism in cells and tissues from bones, intestines, and kidneys. These findings summarize investigations on:

1. Effect of age on Vitamin D receptor binding to rat DNA.
2. Identification of a Ca^{2+} channel in osteoblast-like osteosarcoma cells.
3. Osteosarcoma cells contain a classical L type Ca^{2+} channel.
4. Characterization of the human osteosarcoma cell line CRL-1427 (MG-63) as a model for osteoblastic-like human bone cells.
5. Insulin and insulin like growth factors (IGF-I, II) stimulate Pi transport in cultured renal cells (OK cells).
6. Fluorescent microscopic imaging of cells.
7. Effect of L-triiodothyronine on Na^+/H^+ exchange activity in cultured opossum kidney (OK) cells.
8. Mechanism for the decrease renal ammonia excretion after an acid load in old rats.
9. The effect of thyroid hormones on intestinal transport mechanisms.
10. Pre-steady state studies of Na^+/H^+ exchanger using renal brush border membrane vesicles.
11. Prolactin maintains calcium uptake levels in isolated epithelial cells in male rats.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00052-08 LBC

PERIOD COVERED:

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders)

Regulatory Mechanisms in the Control of Cell Functions

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

Bertram Sacktor	Chief, Laboratory of Biological Chemistry	LBC GRC NIA
Bernard A. Bulos	Research Chemist	LBC GRC NIA
Linda Cheng	Research Chemist	LBC GRC NIA
Charles Filburn	Research Chemist	LBC GRC NIA
J. Kinsella	Research Physiologist	LBC GRC NIA
C. Tony Liang	Research Chemist	LBC GRC NIA
Hiroyuki Hanai	Visiting Fellow	LBC GRC NIA
Hiromichi Kumagai	Visiting Fellow	LBC GRC NIA

COOPERATING UNITS (if any)

M. Levine	Endocrine Division, Department of Medicine, Johns Hopkins Univ.
M. Goldman	Parathyroid Lab., Merck, Sharp, & Dohme, Res. Lab, West Point PA.
J. Handler	Lab. Kidney & Electrolyte Met., Nat. Heart, Lung & Blood Ins, NIH Bethesda, MD

LAB/BRANCH

Gerontology Research Center, Laboratory of Biological Chemistry

SECTION

Regulatory Mechanisms Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS

12.2

PROFESSIONAL

9.1

OTHER

3.1

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This report describes studies on the biochemical and physiological mechanisms by which cell functions are regulated by hormones, agonists, and in pathophysiological states, including aging. The findings summarize investigations on:

1. Age-associated changes in gene expression of the α subunits of GTP-binding proteins in rat renal cells.
2. Purification and quantitation of α_1 subunits of GTP binding protein in the renal cortex.
3. adrenergic regulation of cAMP production in OK cells.
4. Desensitization of OK cells to PTH.
5. Relationship of PTH responsiveness in isolated nephron segments with age.
6. Neurotransmitter regulation of cytosolic Ca^{2+} in bone cells.
7. Regulation of protein kinases C and A in OK cells.
8. PTH and purinergic regulation of cytosolic Ca^{2+} in OK cells.
9. Age-associated changes in hormonal of cytosolic Ca^{2+} in proximal tubules in female rats.
10. Purinergic regulation of cytosolic Ca^{2+} in proximal tubules.
11. Protein kinase C regulation of hormonal responsiveness in proximal tubules.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00048-14 LBC

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Ion Transport Mechanisms and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Jeffrey P. Froehlich Medical Officer, Chief, Membrane Biol Sec LBC GRC NIA

Other:

Phillip F. Heller Chemist LBC GRC NIA

Kinya Otsu Visiting Fellow (EOD 12/1/84) LBC GRC NIA

Sandra Guggino Senior Staff Fellow LBC GRC NIA

Bertram Sacktor Chief, Laboratory of Biological Chemistry LBC GRC NIA

James Kinsella Research Physiologist LBC GRC NIA

cont'd

COOPERATING UNITS (if any)

Department of Physiology, University of Virginia School of Medicine

Laboratory of Neurochemistry, NINCDS, NIH, Bethesda, MD.

Max-Planck Institut für Biophysik, Frankfurt, Germany

LAB/BRANCH

Gerontology Research Center, Laboratory of Biological Chemistry

SECTION

Membrane Biology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS

3.9

PROFESSIONAL

3.2

OTHER:

0.7

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This report describes investigations on ion transport mechanisms and the functional alterations in these mechanisms that occur with aging. These results summarize investigations on:

1. Efficiency of energy coupling declines with age in cardiac muscle sarcoplasmic reticulum.
2. Diminished Ca^{2+} transport efficiency in sarcoplasmic reticulum accompanies the removal of a 53 kDa glycoprotein.
3. Calcium-induced Ca^{2+} release in cardiac sarcoplasmic reticulum is unaltered with age.
4. Polypeptide chain interactions are not essential for active Ca^{2+} transport in skeletal muscle sarcoplasmic reticulum.
5. Interaction of ATP with a low affinity regulatory site on the SR Ca^{2+} pump prevents polypeptide chain interactions during the Ca^{2+} transport cycle.
6. Activation of the Na^+/H^+ exchanger by internal H^+ changes the functional subunit composition of the exchanger.
7. Sodium translocation by the Na, K pump involves a fast conformational transition.
8. Yohimbine and related positively charged alkaloids block the selectivity filter of Ca^{2+} -activated K^+ channels.

ANNUAL REPORT OF THE LABORATORY OF CARDIOVASCULAR SCIENCE

NATIONAL INSTITUTE OF AGING

The overall goals of the Laboratory of Cardiovascular Science are (1) to identify age-related changes that occur within the cardiovascular system and to determine the mechanisms for these changes; (2) to study myocardial structure and function, and response to pharmacological therapeutics in mechanical overload, altered thyroid state, and physical conditioning models, and to determine how age interacts with these chronically altered cardiac states to determine the level of myocardial function; and (3) to study basic mechanisms in excitation-contraction coupling and of energy-yielding oxidative pathways in cardiac muscle. In meeting these objectives, studies are performed in human volunteers, intact animals, isolated heart and vascular tissues, isolated cardiac cells, and subcellular organelles.

Studies in Man

Factors Determining Maximal Exercise Performance in Man. Radionuclide ventriculography and oxygen consumption (VO_2) measurements during maximal upright bicycle ergometry revealed that the markedly (49%) augmented aerobic capacity of endurance trained seniors (mean age = 64 yrs) is due primarily to peripheral rather than central adaptations. These results reinforce our recent finding in 184 untrained Baltimore Longitudinal Study of Aging (BLSA) subjects that the age-associated decline in $\text{VO}_{2\text{max}}$ markedly attenuated after $\text{VO}_{2\text{max}}$ was normalized for total muscle mass instead of body weight.

Age-Related Changes in Cardiac Structure and Function. An analysis of 2-dimensional echocardiograms in normotensive BLSA subjects has shown that the age-associated left ventricular (LV) hypertrophy previously reported by our laboratory is mediated largely by increase in systolic blood pressure (SBP) seen with advancing age. When radionuclide derived LV volumes and echocardiographic LV wall thicknesses are adjusted for body surface area and SBP, there is no distinct gender difference in cardiac structure or function.

Exercise-Induced Arrhythmias in Normal Volunteers. An analysis of 80 asymptomatic BLSA subjects with exercise-induced frequent or repetitive ventricular ectopic beats has revealed a low prevalence of exercise-induced silent ischemia and a very low incidence of cardiac events over a mean followup of 4.6 years. A subset of 31 BLSA subjects with exercise-induced nonsustained ventricular tachycardia (VT) demonstrated a blunting of the normal exercise-related shortening of the QT interval, suggesting a possible mechanism for VT in these apparently healthy subjects.

Detection and prognosis of Silent Myocardial Ischemia. Among 726 asymptomatic BLSA volunteers who have undergone repeated exercise treadmill testing since 1969, serial conversion from a negative to a positive exercise ECG is of no greater predictive value for a future coronary event than in an initially positive response. Twenty-one BLSA subjects with exercise-induced silent myocardial ischemia by treadmill ECG and thallium scan showed no difference in exercise duration, maximal heart rate or peak SBP compared with nonischemic BLSA controls.

Studies in Animal Models

Excitation-Contraction Mechanisms in Isolated Cardiac Cells. Contractile, electrophysiological, and biochemical characteristics are studied in dissociated cardiac cells from adult rats, rabbits and guinea pigs. We have developed a system for simultaneous measurement of changes in cytosolic free $[Ca^{2+}]$, cell length and membrane current/voltage, with high time resolution. The system uses the fluorescent probe Indo-1 to monitor cytosolic free $[Ca^{2+}]$ transient. Cells length is measured from the bright-field image of the cell by an optical edge tracking method using a video edge detector and the membrane potential can be monitored simultaneously with patch electrodes. Salient recent results include the demonstration that (1) Ca^{2+} currents rather than depolarization per se or other depolarization mediated events are required to trigger Ca^{2+} release from the sarcoplasmic reticulum (SR) to cause the rapid increase in cytosolic $[Ca^{2+}]$ (Ca_i) that initiates the twitch contraction; (2) the slow terminal relengthening phase of a twitch contraction coincides in time with a slow decay of Ca_i ; (3) prolonging the duration of depolarization reverses the negative staircase of Ca_i transients and contraction observed upon stimulation of rat myocytes from rest, presumably by augmenting the cell Ca^{2+} load.

Pathophysiologic Effects of Spontaneous Ca^{2+} Release in the Heart. We tested the hypothesis that the occurrence of spontaneous Ca^{2+} release from the SR in the cardiac diastole might be a mechanism for the saturation of systolic contractile function upon exposure to inotropic perturbations that increase cell Ca^{2+} loading. In rat myocytes in the steady state we observed that regardless of drugs or the stimulation frequency, the bathing $[Ca^{2+}]$ (Ca_o) at which the twitch amplitude saturated varied linearly with the Ca_o at which spontaneous Ca^{2+} release first occurred, and this relationship conformed to a line of identity ($r = 0.90$, $PP = <0.001$, $n = 25$). In the transient state following previous stimulation the extent of rest potentiation of the twitch amplitude in rat myocytes was also limited by the occurrence of spontaneous Ca^{2+} release. A mathematical model that incorporates this interaction between potential-mediated SR Ca^{2+} release and the occurrence of spontaneous Ca^{2+} release in individual cells was constructed to predict the behavior of intact multicellular muscle and the behavior of intact muscle was then examined.

The microscopic, myofilament motion caused by spontaneous SR Ca^{2+} release produces scattered light intensity fluctuations (SLIF) in a laser beam scattered by the tissue; SLIF frequency increases with Ca^{2+} loading of resting muscle. Using novel time gated SLIF we studied the relationship of spontaneous SR Ca^{2+} release and resting and twitch tension during time-gated intervals following electrical stimulation or at rest in intact rat and rabbit papillary muscles. In a given muscle the maximum twitch amplitude occurs at approximately the same level of SLIF: when this level is exceeded, either transiently during monotonic or oscillatory recovery following stimulation in a given Ca_o , or in the steady rested state by an increase in Ca_o , twitch tension decreases. The shape of both the transient Ca_o -twitch and rest tension relationship following stimulation and that in the steady state observed in our studies in intact muscle was predicted by the model derived from data in individual cells. Thus, the occurrence of spontaneous SR Ca^{2+} release is a plausible mechanism for the saturation of the inotropic response to Ca^{2+} in the intact myocardium.

Diminished Cardiac Response to Chronic Volume Overload in Older Adult Rats. The effects of long term hemodynamic overload in middle-aged or older animals is

unclear because most studies have used relatively young animals or, when older ones were used, did not compare different age groups with the same duration of the hemodynamic load. There is good reason to believe that the adaptive process of hypertrophic growth may be modified by the age of the animal. Atrioventricular block causes a volume overload state that can be tolerated for long periods of time and induces considerable cardiac hypertrophy that can be related to the amount which the heart rate is slowed. To examine the effect of this type of chronic hemodynamic overload in animals of different ages, we used closed chest electrocautery to induce complete block in male, Sprague-Dawley rats of 5, 12, and 16 months of age for mean duration of 7 months. The results indicate aging over this adult period modified the influence of long term block on cardiac size and the function of isolated cardiac muscle. Chronic block: (1) caused cardiac hypertrophy that was greater in the younger than older animals; (2) prolonged contraction duration that was correlated with the extent of hypertrophy regardless of age and (3) resulted in age-related alterations in contractile function of isolated intact and "chemically skinned" muscle, with the youngest block have more force than control and the older block having equal or less force than control. Differences between younger and older block in both excitation-contraction coupling and myofilament force production are required to explain the observed results. These findings indicate an age-related difference in the chronic myocardial adaptive response to chronic atrioventricular block. The age-related differences in force development in the present study cannot be attributed to the age-related differences in hypertrophy. The ultimate explanation for these findings will require a better understanding of how the myocardium "restructures" itself under the influence of any given hemodynamic stress and how aging affects this process.

Beta-Adrenergic Modulation of Cardiac Function. Beta-adrenergic agonists increase the myocardial contraction amplitude and enhance relaxation. Our studies examine the autonomic modulation of the Ca^{2+} -myofilament interaction to determine whether it could account for enhanced twitch relaxation. In single cardiac myocytes we found that for a given amplitude of Ca_i twitch amplitude was less in isoproterenol (Iso) than in control. In myocyte suspensions norepinephrine (NE, 10 μM) increased troponin-I phosphorylation fourfold and under similar conditions decreased twitch relaxation time in individual myocytes by 20%. After propranolol (1.0 μM) troponin slowly dephosphorylated (half time 16.9 $\pm$ 1.7 min) but relaxation time fully returned to control within 5 min. Thus, the extent of troponin-I phosphorylation by NE is not directly proportional to its effect on relaxation time.

In isolated, aequorin-injected ferret cardiac muscle the Ca^{2+} tension relation was determined from the peak aequorin luminescence and peak tension measured across a broad range of bathing Ca_o in the presence and absence of acetylcholine (ACh, 1 μM) or Iso (1 μM) or both drugs. ACh shifted the relationship of peak tension to (peak) aequorin light leftward, suggesting an increase in myofilament Ca^{2+} sensitivity, but did not alter twitch relaxation ($t_{1/2R}$). Iso shifted the relationship of peak tension to peak aequorin light rightward and decreased $t_{1/2R}$. ACh added to Iso abolished the Iso effect on peak tension-aequorin light relationship but did not reverse the effect of Iso to decrease $t_{1/2R}$. Thus perturbations of the apparent myofilament Ca^{2+} interaction in the intact muscle do not necessarily relate to twitch relaxation time.

Mechanisms of Anoxic Contractile Failure in Cardiac Myocytes. Anoxia of the heart causes failure of contraction prior to any irreversible injury. The

mechanism by which anoxia blocks cardiac excitation-contraction coupling is unknown. Studies in whole muscle are confounded by heterogeneity; however it has not previously been possible to achieve the low oxygen tensions required to study anoxia in single myocytes during electrophysiology recordings. Guided by calculations of oxygen transport, we developed a system in which myocytes in an open dish are insulated from oxygen by a laminar counterflowing column of argon, permitting free access by microelectrodes while maintaining a PO_2 less than 0.02 torr. In the absence of glucose, the amplitude of stimulated contraction of anoxic ventricular myocytes fell to zero over two minutes, after a lag period attributable to consumption of endogenous glycogen. The Ca_i transient, measured by Indo-1 fluorescence, fell to zero simultaneously with the contraction. After the twitch had failed, microinjection of caffeine around the cell still caused a large Ca^{2+} release and contraction, indicating that SR Ca^{2+} stores were not depleted. Failure of the twitch was accompanied by shortening and then failure of the action potential; under voltage clamp, large outward currents, reversing at the resting potential, developed during contractile failure. After failure of action potential-mediated contraction, voltage clamp depolarization, using a large command voltage to compensate for the series resistance error due to the outward currents, restored a normal twitch contraction. We conclude that anoxic contractile failure in the rat myocyte is due to alteration of the action potential, and the distal pathways of excitation-contraction coupling remain essentially intact.

Mechanisms of Ethanol Depression of Myocardial Contractility. The mechanisms of acute ethanol depression of myocardial contractility were examined in intact hearts, isolated cardiac muscle and in suspensions in individual isolated cardiac myocytes. In the isolated, rat heart, ethanol (0.75 - 6.0 vol%) caused a concentration-dependent decline in developed pressure without a change in ATP (adenosine triphosphate), phosphocreatine, inorganic phosphate, or pH measured by NMR techniques. The functional decline could be rapidly and completely reversed by perfusing the ethanol-free solution and significantly, although not completely, reversed by increasing perfusate Ca^{2+} to 4 mM. In single rat cardiac myocytes and myocyte suspensions the acute effects of ethanol (1-5%) on Ca_i transient and contraction and on SR Ca^{2+} content were examined. During stimulation at 1 Hz ethanol decreased the amplitude of the Ca_i transient and decreased the amplitude of contraction. The Ca_i transient amplitude was decreased to a lesser extent than the contraction amplitude. In myocyte suspensions, ethanol caused a concentration dependent initial increase in Ca_i and a subsequent depletion of SR Ca^{2+} content, manifest as a diminution in the Ca_i increase elicited by caffeine in the presence of extracellular EGTA and zero added Ca^{2+} . Thus, in rat cardiac myocytes high ethanol concentrations induces SR Ca^{2+} release and depletes the SR of Ca^{2+} , attenuates the Ca_i transient elicited by electrical stimulation and alters the myofilament Ca^{2+} interaction possibly due to a decrease in myofilament Ca^{2+} sensitivity. These combined effects contribute to the high concentration ethanol depression of contraction. In additional studies in isolated ferret cardiac muscle the threshold ethanol concentration ($0.15 \pm 0.05\%$) which produced a 10% decline in contractile force did not change the Ca_i transient. This decline in contraction strength with no change in Ca_i transient suggests that the negative inotropic effect of low concentrations of ethanol, i.e. to clinically relevant doses, is due to an altered myofilament response to Ca^{2+} .

Effect of Polyamines on Isolated Ventricular Myocytes. Polyamines have been shown to be present in many cell types and their concentration within the tissue

changes in response to a variety of stimuli. β -adrenergic stimulation and hypoxia are associated with an increase in the activity of ornithine decarboxylase, the enzyme responsible for the formation of polyamines, while aging is associated to a decrease in the activity of that enzyme. Additionally, it has been suggested that polyamines may modulate the inotropic state of the myocardium and in particular its response to β -adrenergic stimulation. We have attempted to define the role of polyamines in cardiac muscle.

Isolated rat ventricular myocytes were used to investigate the effect of putrescine, spermidine and spermine on the twitch and the associated Ca_i^{2+} transient and, in the unstimulated state, on the frequency of spontaneous Ca_i^{2+} release from the SR and on resting Ca_i . While putrescine had no effect on contraction and Ca_i , spermidine and spermine had a negative inotropic effect which was due to a decrease in the Ca_i transient and not to a change in myofilament responsiveness to Ca_i . In the unstimulated state there was no effect of spermine either on spontaneous SR Ca_i^{2+} release or on resting Ca_i .

Effect of Alpha_1 -Adrenergic Stimulation of Isolated Ventricular Myocytes. The effect of alpha_1 -adrenergic stimulation on the inotropy of the myocardium is still controversial. A positive inotropic effect has been well documented and it is often preceded by a short lived decrease in contractility. Additionally a persistent negative inotropic effect of alpha_1 stimulation has also been described in multicellular cardiac preparations. The purpose of this study was to characterize the effect of alpha_1 stimulation on the Ca_i transient and on the contractile properties of single ventricular myocytes under condition leading either to an enhancement or a decrease in twitch amplitude.

Isolated rat ventricular myocytes, pretreated with propranolol were used to investigate the effect of alpha_1 -adrenergic stimulation with phenylephrine on twitch amplitude and on the frequency of spontaneous contractile waves, which represent the mechanical expression of spontaneous Ca_i^{2+} release from the SR. In 1 mM bathing Ca_o , during field stimulation at 0.2 Hz, alpha_1 had a positive inotropic effect which was reversibly abolished by prazosin and to a considerable extent appeared related to an increased myofilament responsiveness to Ca_i^{2+} in addition to some enhancement in the amplitude of the Ca_i transient associated with the twitch. b. During stimulation at 0.2 Hz, in 5 mM Ca_o , contractile waves appeared in some of the diastolic intervals. Phenylephrine abolished them and decreased twitch amplitude. This negative effect was in contrast to the positive action observed in parallel studies in 1 mM Ca_o . In similar experiments with myocytes loaded with the Ca_i^{2+} probe Indo-1 AM⁰ the negative effect of alpha_1 on twitch amplitude was associated with a decrease in the amplitude of the Ca_i transient. c. In the absence of stimulation, in 5 mM Ca_o , alpha_1 significantly and reversibly reduced contractile wave frequency. This effect could be prevented by the alpha_1 blocker prazosin. These findings are consistent with the view that the effect of alpha_1 -adrenergic stimulation of cardiac cells can vary in relation to intracellular $[\text{Ca}_i^{2+}]$.

Mechanism of Action of Antidiuretic Hormone. Antidiuretic hormone (ADH) increases the permeability of the distal nephron to water. Water reabsorption in this part of the kidney occurs in response to ADH provided an osmotic gradient from tubule lumen to blood is present. The toad urinary bladder has been used extensively as a structural and functional analogue of the distal nephron for assessing the mechanism of action through which the hydrosmotic response to ADH is achieved. This tissue was used in the present study to

evaluate the possibility that ADH action involves regulation of water permeability not only by altering the luminal plasma membrane barrier of cells forming the mucosal surface of this tissue, but also regulation of one or more resistances beyond or "distal" to this site. Previous freeze fraction studies which have defined luminal membrane water permeability in morphologic terms, suggest that this may be a valid hypothesis. The current experiments demonstrate directly the validity of this hypothesis and provide insight about the functional nature of the intramembrane structural entities that gain appearance in the luminal membrane in response to ADH and are considered as sites for the transluminal membrane water movement.

Cellular Ca^{2+} Ion Homeostasis and the Impact of Aging. This project constitutes an investigation into mechanisms whereby cells achieve the homeostasis of cytosolic free Ca^{2+} concentrations ($[\text{Ca}^{2+}]_c$), and allow perturbations in $[\text{Ca}^{2+}]_c$ in response to hormones and neurotransmitters. Further, it addresses derangements in these control mechanisms which may occur in old-age. This year, we have asked the following questions. (1) What is the mechanism whereby the hormone glucagon leads to an increase in $[\text{Ca}^{2+}]_c$ in hepatocytes? We have investigated the phosphorylation of proteins in a cellular fraction enriched in plasma membrane, on treatment with either cyclic-AMP or exogenous protein kinase A, in a procedure which mimics exposure of the cell to glucagon. Direct correlation between such phosphorylation events and changes in plasma membrane permeability to Ca^{2+} is not yet possible, however. (2) Are there correlates at the level of protein phosphorylation of the previously described decreased responsiveness of contractility to catecholamines in the aging heart? We have quantitated a decreased phosphate content of the proteins troponin-I and C-protein, on exposure of isolated cardiac myocytes to norepinephrine, when cells from senescent animals are compared to those from young adults. This is linked to an inferred decreased net formation of cyclic-AMP, in cells from the senescent animals. This may be expected to have an impact also on sarcolemmal and SR proteins responsible for Ca^{2+} transport. (3) Does ATP, which is released on sympathetic stimulation together with norepinephrine, have a positive inotropic effect, linked to mobilization of $[\text{Ca}^{2+}]_c$, when added at appropriate levels to isolated cardiac myocytes? Micromolar concentrations of exogenous ATP were found to be as potent a positive inotrope as norepinephrine, at the same concentrations, and to give rise to an enhanced transient in $[\text{Ca}^{2+}]_c$ on electrical stimulation. The pharmacology of the response was studied with other purine nucleotides and analogs.

Role of Calcium in the Regulation of Energy Metabolism. This project is designed to assess the physiological importance of Ca^{2+} ions in the regulation of energy metabolism. The activation of muscle contraction by Ca^{2+} ions initiates the performance of intense work and establishes a demand for the more rapid synthesis of ATP. We have shown previously that the increased availability of Ca^{2+} ion to the mitochondria allows the activation of three dehydrogenases, viz pyruvate, isocitrate and 2-oxoglutarate dehydrogenases, which catalyse non-equilibrium steps in the terminal pathway of substrate oxidation. This allows the more rapid generation of NADH and, theoretically at least, minimizes the degree to which the tissue adenine nucleotide phosphorylation potential falls due to increased tissue work, i.e. actomyosin ATP-ase. We have characterized this metabolic linkage by using the term "excitation-contraction-metabolism coupling." In previous years, we have established a relationship between the free Ca^{2+} ion concentration outside the mitochondria and the degree of activation of the intramitochondrial enzyme pyruvate dehydrogenase. This year,

we have taken advantage of the newly-available fluorescent Ca^{2+} -chelating agents to obtain a measure of intramitochondrial free Ca^{2+} concentration directly, and have related this to the degree of enzyme activation. As part of this investigation we have varied the availability of effectors of the mitochondrial Ca^{2+} transport cycle, viz Na^+ and Mg^{2+} ions, and have studied the consequences for the magnitude of the Ca^{2+} gradient across the mitochondrial membrane. In another study, we have measured the degree of activation of pyruvate dehydrogenase as a function of the rate of electrical stimulation of isolated, perfused guinea pig hearts: enzyme activation status increases modestly with increased frequency, but more convincingly when the heart is also made to perform external work. When mitochondria are isolated from these hearts in a rapid protocol designed to prevent changes in the mitochondrial Ca^{2+} content, increased frequency of electrical stimulation is found to correlate with increased mitochondrial Ca^{2+} content. As the significance of dehydrogenase activation lies in the NADH/NAD^+ ratio which can be maintained in the face of elevated work-loads, we have also initiated a study in which we have measured the ratio NADH/NAD^+ in suspensions of rat heart mitochondria with saturating and non-saturating concentrations of pyruvate or 2-oxoglutarate as respiratory substrate, in the presence or absence of Ca^{2+} , and correlated this with the flux through oxidative phosphorylation. Basically, there is a straight-line relationship between the two parameters: anomalies seen in the presence of Ca^{2+} may reveal Ca^{2+} -dependent enzymes other than the dehydrogenases enumerated above.

A long-standing interest of this Section is the impact of aging upon oxidative processes. We have shown previously that there is a specific decrement which develops in old-age in the ability of rat heart mitochondria to oxidize acylcarnitine substrates. This year we have probed the effect of physical training on the ability of canine heart mitochondria to oxidize these substrates.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00029-11 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders)

Efficacy of Digitalis in Congestive Heart Failure and in Normal Subjects

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: J. L. Fleg Staff Cardiologist LCS, NIA

Others: E. G. Lakatta Chief LCS, NIA

COOPERATING UNITS (if any)

Division of Cardiology, Francis Scott Key Medical Center, Baltimore, MD (S. H. Gottlieb), Peter Bent Brigham Hosp., Boston, MA (T. Smith), University of Arizona, Tucson, AZ (F. Marcus), Massachusetts General Hospital, Boston, MA (R. Johnson), Duke University, Durham, NC (H. Strauss and M. Hlatky)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

0.2

PROFESSIONAL:

0.1

OTHER:

0.1

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We have previously shown in a double-blind crossover study that digitalis could be discontinued for three months without adverse clinical effect and only minor changes in cardiac size and function in 30 subjects with stable congestive heart failure (CHF) and sinus rhythm. To assess the ability of maintenance digoxin therapy to improve exercise tolerance in patients with stable CHF, systolic dysfunction and sinus rhythm, we performed maximal treadmill exercise tests in 12 such individuals while monitoring respiratory gas exchange. No difference in exercise duration, maximal oxygen consumption ($\dot{V}O_{2\max}$), maximal heart rate, or ventilation was found after 4 weeks of digoxin versus 4 weeks of placebo in a randomized crossover study. During maximal upright bicycle exercise, however, digoxin increased ejection fraction from .26 to .31 despite identical exercise tolerance. Our group has initiated the development of a questionnaire in conjunction with experts in cardiology at different universities to sample representative groups of academic and practicing physicians in their current use and understanding of the effectiveness and toxicity of digitalis glycosides. Among 2704 questionnaire respondents diuretics alone were considered the best initial therapy for CHF in 50%, digitalis alone by 8% and the combination in 33%. Two thirds of the sample felt that digitalis improved exercise tolerance. Thus, despite growing evidence that digitalis glycosides can be successfully withdrawn from patients with chronic stable CHF, widespread belief persists that these drugs are effective in most CHF patients. Analysis of outpatient laboratory utilization revealed that general/family practitioners saw their CHF outpatients more frequently but were less likely to employ echocardiography or radionuclide ventriculography than were cardiologists, with internists falling in between. Overall annual cost of following a stable CHF outpatient varied from \$621 for general practitioners to \$762 for cardiologists.

Discontinued.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00226-06 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Excitation-Contraction Mechanisms in Isolated Cardiac Cells

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	E. G. Lakatta	Chief	LCS, NIA
Others:	H. A. Spurgeon	Physiologist	LCS, NIA
	M. C. Capogrossi	Medical Officer	LCS, NIA
	M. D. Stern	IPA	LCS, NIA
	D. J. Pelto	Biologist (DOD 7/88)	LCS, NIA

COOPERATING UNITS (if any)

Department of Biology, University of Turku, Turku, Finland (A. Talo); Department of Applied Physiology, University of Cologne, West Germany (G. Isenberg)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

2

PROFESSIONAL:

1.6

OTHER:

0.4

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Contractile, electrophysiological, and biochemical characteristics are studied in dissociated cardiac cells from adult rats, rabbits and guinea pigs. We have developed a system for simultaneous measurement of changes in cytosolic free $[Ca^{2+}]$, cell length and membrane current/voltage, with high time resolution. The system uses the fluorescent probe Indo-1 to monitor cytosolic free $[Ca^{2+}]$ transient. Cell length is measured from the bright-field image of the cell by an optical edge tracking method using a video edge detector and the membrane potential can be monitored simultaneously with patch electrodes. Salient recent results include the demonstration that (1) Ca^{2+} currents rather than depolarization per se or other depolarization mediated events are required to trigger Ca^{2+} release from the sarcoplasmic reticulum to cause the rapid increase in cytosolic $[Ca^{2+}]$ that initiates the twitch contraction; (2) the slow terminal relengthening phase of a twitch contraction coincides in time with a slow decay of cytosolic $[Ca^{2+}]$; (3) prolonging the duration of depolarization reverses the negative staircase of cytosolic $[Ca^{2+}]$ transients and contraction observed upon stimulation of rat myocytes from rest, presumably by augmenting the cell Ca^{2+} load.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00228-05 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Exercise-Induced Arrhythmias in Normal Volunteers

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: J. L. Fleg Staff Cardiologist LCS, NIA

Others: E. G. Lakatta Chief LCS, NIA
J. Busby Guest Researcher LCP, NIA
M. McIvor Medical Staff Fellow (DOD 6/25/87) LCS, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

0.3

PROFESSIONAL:

0.2

OTHER:

0.1

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We have determined the prevalence and significance of exercise-induced frequent or repetitive ventricular ectopic beats (VEB) in apparently healthy BLSA volunteers. Between 1974 and 1984, 80 of 1160 such asymptomatic subjects developed frequent VEB (> 10%) or salvos (≥ 3 in a row) on at least one maximal treadmill exercise test. These 80 subjects were significantly older than the larger group without such exercise-induced VEB (63.8 ± 12.5 vs 50.0 ± 16.1 , $p < .0001$). Only 9 of 80 (11%) demonstrated an ischemic ST segment response to exercise. Over a mean followup of 4.6 years; only 2 cardiac events have occurred.

A prolongation of the QT interval, whether, occurring naturally or induced by drugs or electrolyte imbalance, has been associated with major ventricular arrhythmias. To investigate such an association in apparently healthy subjects, we measured the QT interval at rest (R) maximal exercise (Ex) and recovery (Post EX) in 31 BLSA volunteers with exercise-induced nonsustained ventricular tachycardia (VT) and in 31 BLSA age- and sex-matched subjects without exercise-induced VT. Mean heart rate (beats/min) did not differ between control and VT subjects at rest (72 vs 78), maximal exercise (147 vs 142) or recovery (102 vs 98) respectively. QT intervals ($x \pm \text{SEM}$) were as follows:

	R	EX	Post EX
Control	394 ± 8	275 ± 5	328 ± 5
VT	390 ± 6	302 ± 5	386 ± 12
P	NS	<.001	<.0001

Thus exercise-induced VT in apparently normal subjects is associated with blunted QT interval shortening during exercise, which is accentuated in the recovery period.

(Formerly, Exercise-Induced Cardiac Arrhythmias)

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00231-04 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Role of Calcium in the Regulation of Energy Metabolism

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: R. Hansford Chief, EMBS LSC, NIA

Others: B. Hogue Chemist (EOD 4/88) LCS, NIA
R. Moreno-Sanchez Visiting Fellow LCS, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Energy Metabolism and Bioenergetics Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1.5

PROFESSIONAL:

1.2

OTHER:

0.2

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is designed to assess the physiological importance of calcium ions in the regulation of energy metabolism. We have applied the fluorescent chelating-agent protocol, which was developed for the measurement of cytosolic free Ca^{2+} , to the measurement of mitochondrial matrix free Ca^{2+} ($[\text{Ca}^{2+}]_m$). This allowed us to study directly the relationship between $[\text{Ca}^{2+}]_m$ and the activation of the matrix enzyme pyruvate dehydrogenase for the first time in studies with isolated rat cardiac mitochondria loaded with indo-1. The $K_{0.5}$ for activation was found to be 300 nM Ca^{2+} ; this value was unaffected by procedures, e.g. omission of Mg^{2+} , Na^+ , which change the magnitude of the Ca^{2+} concentration gradient across the mitochondrial membrane. We have also studied the degree of activation of pyruvate dehydrogenase as a function of the rate of electrical stimulation of isolated guinea pig hearts: in a parallel study, mitochondria were rapidly isolated from stimulated hearts, using a protocol which prevents loss or gain of mitochondrial Ca^{2+} and allows us to relate this quantity to the level of dehydrogenase activation. As the significance of dehydrogenase activation lies in the NADH/NAD^+ ratio which can be maintained in the face of elevated work-loads, we have also measured the ratio NADH/NAD^+ in suspensions of rat heart mitochondria with saturating and non-saturating concentrations of pyruvate or 2-oxoglutarate as respiratory substrate, in the presence or absence of Ca^{2+} , and correlated this with the flux through oxidative phosphorylation. Finally, we have examined the ability of cardiac mitochondria from senescent dogs to oxidize substrates (with emphasis on fatty acids) as a function of lifestyle, viz sedentary versus exercised.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00233-04 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Beta-Adrenergic Modulation of Cardiac Function

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	E. G. Lakatta	Chief	LCS, NIA
Others:	M. C. Capogrossi	Medical Officer	LCS, NIA
	H. A. Spurgeon	Physiologist	LCS, NIA
	M. Sakai	Visiting Fellow (DOD 5/88)	LCS, NIA
	R. S. Danziger	Medical Staff Fellow (DOD 7/88)	LCS, NIA
	R. G. Hansford	Chief, EMBS	LCS, NIA
	D. J. Pelto	Biologist (DOD 7/88)	LCS, NIA
	J. M. Staddon	Visiting Fellow, EMBS (DOD 5/88)	LCS, NIA

COOPERATING UNITS (if any)

Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD (M. McIvor)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1.5

PROFESSIONAL:

1.3

OTHER:

.2

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Beta-adrenergic agonists increase the myocardial contraction amplitude and enhance relaxation. Our studies examine the autonomic modulation of the calcium-myofilament interaction to determine whether it could account for enhanced twitch relaxation. In single cardiac myocytes we found that for a given amplitude of cytosolic calcium twitch amplitude was less in isoproterenol (Iso) than in control. In myocytes suspensions norepinephrine (NE, 10 μ M) increased troponin-I phosphorylation fourfold and under similar conditions decreased twitch relaxation time in individual myocytes by 20%. After propranolol (1.0 μ M) troponin slowly dephosphorylated (half time 16.9 $\pm$ 1.7 min) but relaxation time fully returned to control within 5 min. Thus, the extent of troponin-I phosphorylation by NE is not directly proportional to its effect on relaxation time.

In isolated, aequorin-injected ferret cardiac muscle the calcium tension relation was determined from the peak aequorin luminescence and peak tension measured across a broad range of bathing calcium in the presence and absence of acetylcholine (ACh, 1 μ M) or Iso (1 μ M) or both drugs. ACh shifted the relationship of peak tension to (peak) aequorin light leftward, suggesting an increase in myofilament calcium sensitivity, but did not alter twitch relaxation ($t_{1/2R}$). Iso shifted the relationship of peak tension to peak aequorin light rightward and decreased $t_{1/2R}$. ACh added to Iso abolished the Iso effect on peak tension-aequorin light relationship but did not reverse the effect of Iso to decrease $t_{1/2R}$. Thus perturbations of the apparent myofilament calcium interaction in the intact muscle do not necessarily relate to twitch relaxation time.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00239-03 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (At directors or less. Title must fit on one line between the borders.)

Structure and Function of Single Cardiac Myocytes Over a Broad Age Range

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	H. A. Spurgeon	Physiologist	LCS, NIA
Others:	R. Josephson	Medical Staff Fellow	LCS, NIA
	E. G. Lakatta	Chief	LCS, NIA
	M. Sakai	Visiting Fellow	LCS, NIA
	R. S. Danziger	Medical Staff Fellow	LCS, NIA
	D. J. Pelto	Biologist	LCS, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1.5

PROFESSIONAL:

1.4

OTHER:

0.1

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

There has been considerable prior work from this laboratory as well as others documenting that the time course of cardiac contraction in bulk muscle is prolonged with aging. Common measures of inotropy such as the maximal rate or amplitude of tension development appear unchanged with age. However, alterations in the cardiovascular response to stress occur with aging and have been attributed, in part, to a diminished effect of autonomic modulation of cardiovascular function. Whether these measurements represent fundamental characteristics of aging cells or are a reflection of an altered cellular composition of bulk muscle is unclear. Furthermore, what aging-associated alterations, if any, characterize the contractile properties of the fundamental contractile unit, the sarcomere, are unknown. We therefore measured the maximal velocity, amplitude, and time course of unloaded contractions of single isolated cardiac myocytes obtained from rats 2, 8, and 24 months old. We also combined these measurements with data on cell and sarcomere lengths which we have previously determined in similar cells. We find that the prolongation of the time course of contraction that occurs with aging is a fundamental property of the myocyte and must reflect changes in the basic processes governing excitation-contraction coupling. The maximal rate or extent of shortening of individual sarcomeres is unaltered with aging, and the series addition of sarcomeres (which we have previously shown to characterize the aging heart) appears to be an adaptation that may permit the aging heart to meet the challenge of the increased load against which it must function. A decreased contractile response to norepinephrine with adult aging can also be demonstrated directly in cardiac myocytes. This deficit may be specific to catecholamines since the response to a non-adrenergic calcium channel agonist, BayK, is not age-related.

Combined into Z01 AG 00233-04 LCS

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00243-02 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. This must fit on one line between the borders.)

Pathophysiologic Effects of Spontaneous Ca^{2+} Release in the Heart

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: M. C. Capogrossi Medical Officer LCS, NIA

Others: M. D. Stern IPA LCS, NIA
E. G. Lakatta Chief LCS, NIA
H. A. Spurgeon Physiologist LCS, NIA
D. J. Peltz Biologist (DOD 7/88) LCS, NIA

COOPERATING UNITS (if any)

Division of Cardiology, Duke University, Durham, NC (A. A. Kort)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

2.5

PROFESSIONAL:

2.2

OTHER:

0.3

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We tested the hypothesis that the occurrence of spontaneous Ca^{2+} release from the sarcoplasmic reticulum (SR) in the cardiac diastole might be a mechanism for the saturation of systolic contractile function upon exposure to inotropic perturbations that increase cell Ca^{2+} loading. In rat myocytes we observed (1) in the steady state that regardless of drugs or the stimulation frequency, the bathing Ca_0 at which the twitch amplitude saturated varied linearly with the occurrence of spontaneous Ca^{2+} release and (2) in the transient state following previous stimulation the extent of rest potentiation of the twitch amplitude in rat myocytes was also limited by the occurrence of spontaneous Ca^{2+} release. A mathematical model that incorporates this interaction between potential-mediated SR Ca^{2+} release and the occurrence of spontaneous Ca^{2+} release in individual cells was constructed to predict the behavior of intact multicellular muscle.

The microscopic, myofilament motion caused by spontaneous SR Ca^{2+} release in muscles produces scattered light intensity fluctuations (SLIF) in a laser beam scattered by the tissue. Using novel time gated SLIF we studied the relationship of SLIF and tension during time-gated intervals following electrical stimulation. In a given muscle the maximum twitch amplitude occurs at approximately the same level of SLIF: when this level is exceeded, either transiently during monotonic or oscillatory recovery following stimulation in a given Ca_0 , or in the steady rested state by an increase in Ca_0 , twitch tension decreases. This behavior in intact muscle was predicted by the model derived from data in individual cells. Thus, the occurrence of spontaneous SR Ca^{2+} release is a plausible mechanism for the saturation of the inotropic response to Ca^{2+} in the intact myocardium.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00244-02 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Myocardial Calcium Oscillations During Reperfusion and Reoxygenation

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: E. G. Lakatta Chief LCS, NIA

Others: R. G. Weiss Medical Staff Fellow LCS, NIA
M. D. Stern IPA LCS, NIA

COOPERATING UNITS (if any)

Division of Cardiology, Johns Hopkins Medical Institutions (G. Gerstenblith)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1.5

PROFESSIONAL:

1.3

OTHER:

.2

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

The full extent of myocardial contractile recovery following ischemia is delayed beyond the immediate reperfusion (R). This may be associated with delayed metabolic recovery and/or Ca²⁺ overload. This can be quantified in the beating heart by the scattered laser intensity fluctuations (SLIF) which senses Ca oscillations (CaOs) it produces. We measured ATP, and pH by ³¹P NMR and SLIF, and developed pressure in isovolumic rat hearts. During the first 5 min of R there is rapid metabolic but a more gradual developed pressure and SLIF recovery. Then both gradually recover developed pressure abruptly and SLIF increases fourfold over the next 40 min mean no change in metabolic parameters. These findings suggest that delayed contractile recovery during (R) is attributable in part to an adverse effect of increased CaOs induced by Ca²⁺ overload during R. In additional hearts, for the first 10 min of R, perfusate Ca was 1.5mM (Group 1, n=4) or 0.08mM (Group 2, n=4). During R the early peak in SLIF was not present in Group 2. Recovery of DP was higher and cell Ca lower in Group 2 vs Group 1 at 20 min R. Thus, CaOs during early R are modified by perfusate Ca, noninvasively index the extent of Ca loading, and predict functional recovery.

Other hearts were pretreated with Amiloride 10⁻⁴, a known Na-Ca blocker during hypoxia and reoxygenation (ReO₂). During ReO₂, DP, EDP and PCr (all % base-line), and pH_i recovery were improved in the Amiloride treated hearts. Cell gain during ReO₂ was reduced 50% by Amiloride. These results suggest that cell Ca loading during reoxygenation is Na dependent and may be mediated in part by Na/Ca exchange.

Combined into Z01 AG00243-02 LCS.

IRP-LCS-46

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00245-02 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders)

Cardiac Muscle Properties in Senescent Rats is not Related to Serum Urea Levels

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: E. G. Lakatta Chief LCS, NIA

Others: H. A. Spurgeon Physiologist LCS, NIA

COOPERATING UNITS (if any)

Division of Cardiology, Johns Hopkins Medical Institutions (G. Gerstenblith)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

0.3

PROFESSIONAL:

.25

OTHER:

.05

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

One of the most striking changes in the cardiovascular system which accompanies advancing age is the prolongation of the duration of systole. This age-associated prolongation occurs in man, lower mammals, and in rodents, and apparently represents an age related change in cardiac muscle across species. However, advancing age in rodents is also often accompanied by a progressive decline in renal function, making it difficult to partition cardiovascular changes into truly age-related versus renal related declines. In order to determine whether myocardial function in senescent (24 mo) male Wistar rats varies with SUN, we measured function of isolated cardiac muscle from animals with higher and lower SUN. Muscles were bathed in normal Ringer's bicarbonate solution ($[Ca] = 1.0 \text{ mM}$) and stimulated to contract 24 min^{-1} at 30°C at L_{max} . The mean $\pm$ SEM, SUN, resting tension (RT), developed twitch tension (TT), maximum rate of tension rise (dt/dt_{max}) and contraction duration (CD) in the two groups were:

SUN	p<.0001	N	RT (g/mm ²)	TT (g/mm ²)	dt/dt (g/mm ² /max sec)	CD (msec)
60.83 $\pm$ 2.31		6	1.46 $\pm$.28	3.19 $\pm$.46	35.45 $\pm$ 4.88	283 $\pm$ 7
26.14 $\pm$ 1.44		7	1.45 $\pm$.42	3.23 $\pm$.64	36.74 $\pm$ 7.96	290 $\pm$ 8

Thus, these contractile properties of isolated cardiac muscle do not depend on SUN. Additionally, the maximum contractile response to isoproterenol (10^{-5}M) did not vary with SUN ($dt/dt = 34\pm 6$ vs $21\pm 9\%$ control in the high and low SUN group respectively). We conclude that contractile function in cardiac muscle from senescent rats is not affected by the levels of SUN encountered in these rats.

Discontinued.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00246-02 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effect of Alpha₁-Adrenergic Stimulation on Isolated Ventricular Myocytes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	M. C. Capogrossi	Medical Officer	LCS, NIA
Others:	W. A. Kachadorian	Staff Scientist	LCS, NIA
	E. G. Lakatta	Chief	LCS, NIA
	H. A. Spurgeon	Physiologist	LCS, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1

PROFESSIONAL:

.9

OTHER:

.1

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The effect of alpha₁-adrenergic stimulation on the inotropy of the myocardium is still controversial. A positive inotropic effect has been well documented and it is often preceded by a short lived decrease in contractility. Additionally a persistent negative inotropic effect of alpha₁ stimulation has also been described in multicellular cardiac preparations. The purpose of this study was to characterize the effect of alpha₁ stimulation on the cytosolic Ca²⁺ (Ca_i) transient and on the contractile properties of single ventricular myocytes under condition leading either to an enhancement or a decrease in twitch amplitude.

Isolated rat ventricular myocytes, pretreated with propranolol were used to investigate the effect of alpha₁-adrenergic stimulation with phenylephrine on twitch amplitude (TA) and on the frequency of spontaneous contractile waves (CW), which represent the mechanical expression of spontaneous Ca²⁺ release from the sarcoplasmic reticulum (SR). In 1 mM bathing [Ca²⁺] (Ca_o), during field stimulation at 0.2 Hz, alpha₁ had a positive inotropic effect which was reversibly abolished by prazosin and to a considerable extent appeared related to an increased myofilament responsiveness to Ca²⁺ in addition to some enhancement in the amplitude of the Ca_i transient associated with the twitch. b. During stimulation at 0.2 Hz, in 5 mM Ca_o, CW appeared in some of the diastolic intervals. Phenylephrine abolished them and decreased TA. This negative effect was in contrast to the positive action observed in parallel studies in 1 mM Ca_o. In similar experiments with myocytes loaded with the Ca²⁺ probe Indo-1 AM the negative effect of alpha₁ on TA was associated with a decrease in the amplitude of the Ca_i transient. c. In the absence of stimulation, in 5 mM Ca_o, alpha₁ significantly and reversibly reduced CW frequency. This effect could be prevented by the alpha₁ blocker prazosin. These findings are consistent with the view that the effect of alpha₁-adrenergic stimulation of cardiac cells can vary in relation to intracellular [Ca²⁺].

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00247-02 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (60 characters or less. Title must fit on one line between the borders.)

Detection and Prognosis of Silent Myocardial Ischemia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: J. L. Fleg Staff Cardiologist LCS, NIA

Others: A. Zonderman Senior Staff Fellow LPC, NIA
 P. Costa Chief LPC, NIA
 R. Josephson Medical Staff Fellow (DOD 6/88) LCS, NIA
 E. G. Lakatta Chief LCS, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

2.0

PROFESSIONAL:

0.8

OTHER:

1.2

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

726 apparently healthy subjects from the BLSA underwent serial maximal exercise treadmill testing since 1969, the risk of future cardiac events was compared in those whose initial test was positive (Group I) versus those converting from negative to positive (Group II) over a 6.4 year mean followup.

	Group I	Group II	p
n	86	92	
age	64	63	NS
men (%)	63	87	.01
events	17	17	NS
events/100 person-yrs	2.8	3.2	NS

Combining groups I and II, the incidence of future events was 3.5 times as great in the 176 subjects with positive exercise ECG's as in the 548 individuals whose tests were consistently negative.

Thus in asymptomatic subjects, serial conversion from a negative to a positive exercise ECG is of no greater predictive value for a future coronary event than an initially positive response.

To determine the effect of silent myocardial ischemia on maximal exercise performance in totally asymptomatic subjects, we compared exercise duration, maximal heart rate (MHR), systolic blood pressure, and rate-pressure product at maximal treadmill workload in 21 asymptomatic BLSA volunteers (ages 57-81 yrs) who had ischemic ECG and thallium scan responses to maximal treadmill exercise with results in age-matched nonischemic BLSA controls. No differences in any of these parameters were noted between the groups.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00248-02 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Factors Detecting Maximal Exercise Performance in Man

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	J. L. Fleg	Staff Cardiologist	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA
	J. Busby	Guest Researcher	LCP, NIA
	D. Drinkwater	Visiting Fellow	LCP, NIA
	R. Andres	Chief	LCP, NIA
	L. Fried	IPA	LCP, NIA
	J. Tobin	Chief, APS	LCP, NIA
	Frances O'Connor	Chemist	LCS, NIA

COOPERATING UNITS (if any)

Div. Cardiol., Johns Hopkins Hospital (G. Gerstenblith, S. Schulman, L. Becker, M. L. Weisfeldt); Sch. Hygiene, Johns Hopkins Hospital (S. Fortney); Div. Geriat. Med., Francis Scott Key Med. Ctr. (A. Goldberg)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

4.2

PROFESSIONAL:

1.8

OTHER:

2.4

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We have recently demonstrated in 184 non endurance trained non obese men and women from the BLSA with normal maximal exercise ECG's that the age-associated decline in $\dot{V}O_{2\max}$ was markedly attenuated after $\dot{V}O_{2\max}$ was normalized for total muscle mass instead of body weight. These results suggested an important role of peripheral (vs central circulatory) factors in the age-related reduction of maximal aerobic performance.

A closely related issue is whether the well documented marked increase in maximal oxygen-consumption ($\dot{V}O_{2\max}$) of older endurance trained men relative to that of age-matched peers is mediated primarily by central versus peripheral adaptations. We performed radionuclide ventriculography and $\dot{V}O_2$ measurements during maximal upright bicycle ergometry in 8 endurance trained (mean age = 65 ± 5 yr, treadmill $\dot{V}O_{2\max} = 51 \pm 4$ ml/kg/min) and 6 age-matched sedentary (treadmill $\dot{V}O_{2\max} = 31 \pm 4$ ml/kg.min) men. The maximum workload (MWL), the measured $\dot{V}O_2$ at MWL (peak $\dot{V}O_2$) and cardiac output (CO) at MWL and derived average arteriovenous oxygen difference $[(A-V)O_2]$ at MWL are shown below (mean $\pm$ S.D.).

	Endurance Trained	Sedentary	P
MWL (watts)	172 ± 31	129 ± 19	.02
Peak $\dot{V}O_2$ (L/min)	2.27 ± 0.33	1.52 ± 0.30	.003
CO (L/min)	17.6 ± 4.2	15.9 ± 3.4	NS
(A-V) $\dot{V}O_2$ (vol. %)	13.4 ± 2.9	9.9 ± 2.7	.05

Thus, the augmented aerobic capacity of endurance trained seniors at exhaustion during upright bicycle exercise is due primarily to peripheral rather than central adaptations.

IRP-LCS-50

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00249-02 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cellular Ca^{2+} Ion Homeostasis and the Impact of Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: R. G. Hansford Chief, EMBS LCS, NIA

Others: B. Hogue Chemist (EOD 4/88) LCS, NIA
J. Staddon Visiting Fellow (DOD 5/88) LCS, NIA
R. Moreno-Sanchez Visiting Fellow LCS, NIA

COOPERATING UNITS (if any)

Cardiac Function Section, LCS

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Energy Metabolism and Bioenergetics Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1.6

PROFESSIONAL:

1.4

OTHER:

0.2

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

This project constitutes an investigation into mechanisms whereby cells achieve the homeostasis of cytosolic free Ca^{2+} concentrations ($[\text{Ca}^{2+}]_c$), and allow perturbations in $[\text{Ca}^{2+}]_c$ in response to hormones and neurotransmitters. Further, it addresses derangements in these control mechanisms which may occur in old-age. This year, we have asked the following questions. (1) What is the mechanism whereby the hormone glucagon leads to an increase in $[\text{Ca}^{2+}]_c$ in hepatocytes? We have investigated the phosphorylation of proteins in a cellular fraction enriched in plasma membrane, on treatment with either cyclic-AMP or exogenous protein kinase A, in a procedure which mimics exposure of the cell to glucagon. Direct correlation between such phosphorylation events and changes in plasma membrane permeability to Ca^{2+} is not yet possible, however. (2) Are there correlates at the level of protein phosphorylation of the previously described decreased responsiveness of contractility to catecholamines in the aging heart? We have quantitated a decreased phosphate content of the proteins troponin-I and C-protein, on exposure of isolated cardiac myocytes to norepinephrine, when cells from senescent animals are compared to those from young adults. This is linked to an inferred decreased net formation of cyclic-AMP, in cells from the senescent animals. This may be expected to have an impact also on sarcolemmal and sarcoplasmic reticulum proteins responsible for Ca^{2+} transport. (3) Does ATP, which is released on sympathetic stimulation together with norepinephrine, have a positive inotropic effect, linked to mobilization of $[\text{Ca}^{2+}]_c$, when added at appropriate levels to isolated cardiac myocytes? Micromolar concentrations of exogenous ATP were found to be as potent a positive inotrope as norepinephrine, at the same concentrations, and to give rise to an enhanced transient in $[\text{Ca}^{2+}]_c$ on electrical stimulation. The pharmacology of the response was studied with other purine nucleotides and analogs.

IRP-LSC-51

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00250-01 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Age-Related Changes in Cardiac Structure and Function

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	J. L. Fleg	Staff Cardiologist	LCS, NIA
Others:	R. S. Danziger	Medical Staff Fellow	LCS, NIA
	E. G. Lakatta	Chief	LCS, NIA
	S. P. Schulman	Medical Staff Fellow	LCS, NIA
	C. Swinne	Guest Researcher	LCS, NIA

COOPERATING UNITS (if any)

Division of Cardiology, Johns Hopkins Hospital (J. A. Lima, G. Gerstenblith, M. Waclawiw), Division of Cardiology, Frances Scott Key Medical Center (D. Bush)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

2.0

PROFESSIONAL:

1.0

OTHER:

1.0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We have previously shown that left ventricular (LV) wall thickness increases with age in normotensive BLSA men. To determine whether this finding relates to the increase in systolic blood pressure (SBP) which also accompanies normal aging, LV wall thickness (Th) was measured in short axis 2-dimensional echocardiogram (2-D echo) echoes obtained from 74 participants of the Baltimore Longitudinal Aging population without evidence of hypertensive (BP < 140/90) or ischemic heart disease. The average of 3 contiguous septal wall Th measurements normalized for body surface area (WTS) was related to age (WTS = $0.66 + 0.0029 [\text{age}]$, $r = 0.26$, $p < 0.03$), but more strongly to SBP (WTS = $0.32 + 0.0039 [\text{SBP}]$, $r = 0.39$, $p < 0.001$). When WTS was regressed against age and SBP (multivariate analysis) the effect of age became insignificant ($p = 0.28$) while SBP remained a strong determinant of WTS ($r = 0.41$, $p = 0.0045$). These data suggest that the normal LV hypertrophy associated with aging is mediated via an increase in SBP. Doppler echocardiography during isometric handgrip in 25 healthy BLSA subjects revealed that advanced age was associated with a greater rise in systolic blood pressure ($r = .53$, $p = .008$), greater increases in LV end diastolic dimension ($r = .59$, $p = .002$) and end systolic dimensions ($r = .50$, $p = .01$), blunted fractional shortening ($r = .42$, $p = .04$) and a further augmentation of atrial contribution to LV filling ($r = .48$, $p = .014$).

In a related study, MUGA end-diastolic volume (EDV) and ejection fraction (EF) in 47 women (W) and 104 men (M), and average LV end-diastolic wall thickness (EDWT) by 2-D echo (31 W and 43 M) were obtained in BLSA subjects. Both EDV and EDWT were smaller in W than in M (117 ± 30 vs 146 ± 38 ml $p < 0.001$ and 0.97 ± 0.14 vs 1.17 ± 0.16 cm, $p < .001$ respectively). EF was greater in W than in M (68 ± 7 vs $64 \pm 7\%$, $p < .005$). Gender differences were eliminated by adjustment for body surface area (BSA) and systolic blood pressure (SBP). Thus, there is no distinctive gender difference in cardiac structure or function.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00251-01 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Mechanisms of Anoxic Contractile Failure in Cardiac myocytes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI M. D. Stern IPA LCS, NIA

Others	H. S. Silverman	Guest Researcher	LCS, NIA
	R. A. Josephson	Medical Staff Fellow (DOD 6/88)	LCS, NIA
	M. C. Capogrossi	Medical Officer	LCS, NIA
	E. G. Lakatta	Chief	LCS, NIA

COOPERATING UNITS (if any)

Department of Physiology, Temple University, Philadelphia, PA (S. R. Houser),
Department of Physiology, University of Maryland, Baltimore, MD (C. G. Nichols
and W. J. Lederer)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1.5

PROFESSIONAL:

1.4

OTHER:

0.1

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Anoxia of the heart causes failure of contraction prior to any irreversible injury. The mechanism by which anoxia blocks cardiac excitation-contraction coupling is unknown. Studies in whole muscle are confounded by heterogeneity; however it has not previously been possible to achieve the low oxygen tensions required to study anoxia in single myocytes during electrophysiology recordings. Guided by calculations of oxygen transport, we developed a system in which myocytes in an open dish are insulated from oxygen by a laminar counterflowing column of argon, permitting free access by microelectrodes while maintaining a PO_2 less than 0.02 torr. In the absence of glucose, the amplitude of stimulated contraction of anoxic ventricular myocytes fell to zero over two minutes, after a lag period attributable to consumption of endogenous glycogen. The cytosolic calcium transient, measured by Indo-1 fluorescence, fell to zero simultaneously with the contraction. After the twitch had failed, microinjection of caffeine around the cell still caused a large calcium release and contraction, indicating that sarcoplasmic reticulum calcium stores were not depleted. Failure of the twitch was accompanied by shortening and then failure of the action potential; under voltage clamp, large outward currents, reversing at the resting potential, developed during contractile failure. After failure of action potential-mediated contraction, voltage clamp depolarization, using a large command voltage to compensate for the series resistance error due to the outward currents, restored a normal twitch contraction. We conclude that anoxic contractile failure in the rat myocyte is due to alteration of the action potential, and the distal pathways of excitation-contraction coupling remain essentially intact.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00252-01 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Mechanisms of Ethanol Depression of Myocardial Contractility

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: E. G. Lakatta Chief LCS, NIA

Others: R. S. Danziger Medical Staff Fellow (DOD 7/88) LCS, NIA
M. C. Capogrossi Medical Officer LCS, NIA
M. Sakai Visiting Fellow (DOD 4/88) LCS, NIA
S. Schulman Medical Staff Fellow LCS, NIA
O. Hano Guest Researcher LCS, NIA
S. Raffaelli Guest Researcher (DOD 12/87) LCS, NIA

COOPERATING UNITS (if any)

Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD (T. Guarnieri and G. Gerstenblith)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

3.0

PROFESSIONAL:

2.9

OTHER:

.1

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The mechanisms of acute ethanol depression of myocardial contractility were examined in intact hearts, isolated cardiac muscle and in suspensions in individual isolated cardiac myocytes. In the isolated, rat heart, ethanol (0.75 - 6.0 vol%) caused a concentration-dependent decline in developed pressure without a change in ATP (adenosine triphosphate), phosphocreatine, inorganic phosphate, or pH measured by NMR techniques. The functional decline could be rapidly and completely reversed by perfusing the ethanol-free solution and significantly, although not completely, reversed by increasing perfusate calcium to 4 mM. In single rat cardiac myocytes and myocyte suspensions the acute effects of ethanol (1-5%) on cytosolic $[Ca^{2+}]$ (Ca_i) transient and contraction and on sarcoplasmic reticulum (SR) calcium content were examined. During stimulation at 1 Hz ethanol decreased the amplitude of the Ca_i transient and decreased the amplitude of contraction. The Ca_i transient amplitude was decreased to a lesser extent than the contraction amplitude. In myocyte suspensions, ethanol caused a concentration dependent initial increase in Ca_i and a subsequent depletion of SR calcium content, manifest as a diminution in the Ca_i increase elicited by caffeine in the presence of extracellular EGTA and zero added calcium. Thus, in rat cardiac myocytes high ethanol concentrations induces SR calcium release and depletes the SR of calcium, attenuates the Ca_i transient elicited by electrical stimulation and alters the myofilament calcium interaction possibly due to a decrease in myofilament calcium sensitivity. These combined effects contribute to the high concentration ethanol depression of contraction. In additional studies in isolated ferret cardiac muscle the threshold ethanol concentration (0.15±0.05%) which produced a 10% decline in contractile force did not change the Ca_i transient. This decline in contraction strength with no change in Ca_i transient suggests that the negative inotropic effect of low concentrations of ethanol is due to an altered myofilament response to calcium.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00253-01 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Diminished Cardiac Response to Chronic Volume Overload in Older Adult Rats

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: H. A. Spurgeon Physiologist LCS, NIA

Others: E. G. Lakatta Chief LCS, NIA

COOPERATING UNITS (if any)

Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD (G. W. Walford)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1.2

PROFESSIONAL:

1.2

OTHER:

0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unindented type. Do not exceed the space provided.)

The effects of long term hemodynamic overload in middle-aged or older animals is unclear because most studies have used relatively young animals or, when older ones were used, did not compare different age groups with the same duration of the hemodynamic load. There is good reason to believe that the adaptive process of hypertrophic growth may be modified by the age of the animal. Atrioventricular block (B) causes a volume overload state that can be tolerated for long periods of time and induces considerable cardiac hypertrophy that can be related to the amount which the heart rate is slowed. To examine the effect of this type of chronic hemodynamic overload in animals of different ages, we used closed chest electrocautery to induce complete B in male, Sprague-Dawley rats of 5, 12, and 16 months of age for mean duration of 7 months. The results indicate aging over this adult period modified the influence of long term B on cardiac size and the function of isolated cardiac muscle. Chronic B: (1) caused cardiac hypertrophy that was greater in the younger than older animals; (2) prolonged contraction duration that was correlated with the extent of hypertrophy regardless of age and (3) resulted in age-related alterations in contractile function of isolated intact and "chemically skinned" muscle, with the youngest B have more force than control (C) and the older B having equal or less force than C. Differences between younger and older B in both excitation-contraction coupling and myofilament force production are required to explain the observed results. These findings indicate an age-related difference in the chronic myocardial adaptive response to chronic atrioventricular B. The age-related differences in force development in the present study cannot be attributed to the age-related differences in hypertrophy. The ultimate explanation for these findings will require a better understanding of how the myocardium "restructures" itself under the influence of any given hemodynamic stress and how aging affects this process.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00254-01 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effect of Polyamines on Isolated Ventricular Myocytes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I. C. Ferroni Guest Researcher LCS, NIA

Others: E. G. Lakatta Chief LCS, NIA

M. C. Capogrossi Medical Officer LCS, NIA

COOPERATING UNITS (If any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

.5

PROFESSIONAL:

.5

OTHER:

.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Polyamines have been shown to be present in many cell types and their concentration within the tissue changes in response to a variety of stimuli. β -adrenergic stimulation and hypoxia are associated with an increase in the activity of ornithine decarboxylase, the enzyme responsible for the formation of polyamines, while aging is associated to a decrease in the activity of that enzyme. Additionally, it has been suggested that polyamines may modulate the inotropic state of the myocardium and in particular its response to β -adrenergic stimulation. We have attempted to define the role of polyamines in cardiac muscle.

Isolated rat ventricular myocytes were used to investigate the effect of putrescine, spermidine and spermine on the twitch and the associated cytosolic Ca^{2+} (Ca_i) transient and, in the unstimulated state, on the frequency of spontaneous Ca^{2+} release from the sarcoplasmic reticulum (SR) and on resting Ca_i . While putrescine had no effect on contraction and Ca_i spermidine and spermine had a negative inotropic effect which was due to a decrease in the Ca_i transient and not to a change in myofilament responsiveness to Ca_i . In the unstimulated state there was no effect of spermine either on spontaneous SR Ca^{2+} release or on resting Ca_i .

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00255-01 LCS

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders)

Mechanism of Action of Antidiuretic Hormone

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: W. A. Kachadorian

Research Physiologist

LCS, NIA

Others: K. R. Spring

Research Physiologist

LKEM, NHLBI

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

0.2

PROFESSIONAL:

0.1

OTHER:

0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Antidiuretic hormone (ADH) increases the permeability of the distal nephron to water. Water reabsorption in this part of the kidney occurs in response to ADH provided an osmotic gradient from tubule lumen to blood is present. The toad urinary bladder has been used extensively as a structural and functional analogue of the distal nephron for assessing the mechanism of action through which the hydrosmotic response to ADH is achieved. This tissue was used in the present study to evaluate the possibility that ADH action involves regulation of water permeability not only by altering the luminal plasma membrane barrier of cells forming the mucosal surface of this tissue, but also regulation of one or more resistances beyond or "distal" to this site. Previous freeze fracture studies which have defined luminal membrane water permeability in morphologic terms, suggest that this may be a valid hypothesis. The current experiments demonstrate directly the validity of this hypothesis and provide insight about the functional nature of the intramembrane structural entities that gain appearance in the luminal membrane in response to ADH and are considered as sites for transluminal membrane water movement.

NATIONAL INSTITUTE ON AGING

Inorganic Biochemistry Section

Structure at the Active Site of RNA Polymerase. Considerable progress has occurred in our studies on mapping the active site of RNA polymerase to determine the mechanism for internucleotide bond formation during RNA synthesis. The active site consists of the i (initiation) and i+1 (elongation) subsites, each of which is associated with a metal ion and one of the two substrates between which the internucleotide bond is formed. The metal ions have been used as probes to determine the distances between the metals and the substrate at each subsite, and after determining the distance between the metals themselves it was then possible to construct a model in which the geometrical relationship between the two substrates during internucleotide bond formation was represented. Further studies demonstrated that this relationship changed when a DNA template was introduced into the system.

This model has now been further refined, and cross-distances, such as the distance between the α -phosphate of ATP in i and the metal ion in i+1 have been calculated. It was then determined with the Evans and Sutherland graphics that the structure was a unique structure for the distance constraints that had been measured. We have thus increased the accuracy of the model and demonstrated its uniqueness as well.

Having established the configuration of the active site with two ATP molecules in the two subsites, we now set about to determine the relationship between substrates when one of the ATPs, the one in i, was displaced by the dinucleotide ApU, so that i contained ApU and i+1 contained ATP. Distances were measured from the metal in i+1 to the ApU in i. The U in ApU would be expected to be in the same position as the A in ATP in the i site in our previous experiments, yet the distances were rather different from the distances to ATP in the model described above. These results indicate a difference in the active site conformation when ATP is displaced by ApU. This difference could be due to the displacement of A by U, or by the displacement of a mononucleotide by a dinucleotide in the i subsite. In either case, these results indicate that a change in the substrates alters the conformation of the enzyme active site. Thus, we have now demonstrated two conformational changes in the active site of this enzyme, one imposed by the template, and, now, the other imposed by substrate.

Active and Inactive Forms of RNA Polymerase. RNA polymerase (RNAP) from E. coli is routinely purified to gross physical homogeneity. Nevertheless, a substantial proportion of the enzyme molecules in such preparations -- some 50-70% -- commonly behaves as if incompetent for processive elongation. This behavior has been found independently in many laboratories, and suggests but does not prove that inactive enzyme molecules exist in otherwise homogeneous preparations. Indeed, very

little if anything is known about the properties, origin or enzymatic significance of the apparently incompetent molecules. Understanding these aspects of enzyme activity is of particular importance to us because of our interest in the active site of the enzyme, and if possible we would like to purify the enzyme to full competency.

As a first step we analyzed DNA-binding properties of RNAP during the course of RNA synthesis on T7 DNA, for the population of enzyme molecules in typical preparations, by measuring the ability of the enzyme to withstand competitive binding to the polyanion heparin. (Heparin binds RNAP strongly and nonspecifically; T7 DNA contains one block of promoter-coding-terminator sequence recognized by E. coli RNAP.) This analysis shows definitely that elongation-inactive enzyme cores physically exist in enzyme preparations, and indicates that functional, and possibly physical, means of purification of fully active enzyme can be devised.

Three subpopulations of enzyme cores are detected operationally, based on template binding and elongation competency: (a) poor DNA binders that are easily removed onto heparin during stable elongation without any effect on elongation activity; (b) strong DNA binders that do not become heparin-extractable even after the termination phase, and probably are devoid of elongation activity; and (c) strong DNA binders that elongate and terminate with high efficiency. Fraction (c), which consists of the RNAP cores that resist heparin extraction during the elongation phase but subsequently terminate, was found to be greatly enriched in elongation competency over the original preparation and to account for virtually all of the elongation activity expressed.

Metals, Cells and Aging. We have studied uptake and distribution of various metal ions with cellular in vitro age in human diploid fibroblasts. Our recent findings with atomic absorption measurements of copper, aluminum and manganese show a similar approximate 2-4 fold increase in cells with age as we have previously demonstrated with zinc. This increase is significant since it is much greater than the concomitant increase in cell volume, protein or RNA increases.

We have also measured metal distribution in the nucleus vs. cytoplasm of the cell utilizing sub-cellular fractionation, both for untreated cells and cells subjected to excess zinc. These results indicate that although most of the accumulated metal is sequestered in the cytoplasm of the cell, the nucleus also accumulates zinc with age. This finding is consistent with other aging studies, for instance, increased metal levels in isolated chromatin with age.

In Vivo NMR Studies on Exercise in Humans. In the in vivo NMR studies on human aging, the ^{31}P NMR spectrum of human muscle reveals the presence of phosphocreatine (PCr), ATP, inorganic phosphate (P_i), phosphomonoesters (PME) and phosphodiester (PDE), and the changes in the levels of these metabolites as well as intracellular pH can be monitored during and after exercise. A hand dynamometer interfaced to a PC and a display unit is used to monitor subject performance during

30-second exercise periods at 30%, 40%, 50% and 60% of maximum workload with 1 minute rest periods following each exercise. Exercise is also carried out for 3 minutes at 30% of maximum workload, followed by 3 minutes of recovery. ^{31}P NMR spectra of the forearm flexor muscle are collected throughout the exercise and recovery periods, allowing metabolic changes in the muscle to be monitored.

We have found that each additional workload causes further decline in PCr/Pi ratio as well as intracellular pH. After 1-min. of rest, metabolic recovery is still incomplete following 30-sec exercise periods at 50% and 60%. The exercise at 60% workload causes the greatest degree of lactic acidosis.

We have also found that exercise at a constant workload of 30% for 3 minutes produces a dramatic decline in PCr/Pi as well as intracellular pH. During the subsequent recovery period, PCr/Pi is restored to normal levels after 3 minutes, but the recovery of intracellular pH is incomplete. After a 3-min. recovery period some subjects are unable to perform a second 3-minute exercise at 30% of the max workload. Thus a component of fatigue is independent of PCr/Pi and may be related to intracellular pH.

MOLECULAR DYNAMICS SECTION

Hypoxic Stress. Our earlier observation that hypoxic conditions result in the leakage of superoxide from the erythrocyte has been actively pursued. Initial studies with myocytes and fibroblasts suggest that low pressure incubation with erythrocytes influence the viability of these cells. Prior to a more extensive investigation of the potential damage inflicted by hypoxic erythrocytes we have initiated a series of studies designed to define the origin of the oxyradicals generated in erythrocytes and the conditions which optimize this hypoxic stress.

Purified Hemoglobin. Autoxidation of hemoglobin coincides with the formation of superoxide radicals. Although it has been reported that autoxidation is enhanced at low oxygen pressures, the explanation of this unusual phenomenon has not been explained. We have undertaken a detailed investigation of the rate of hemoglobin oxidation as a function of the oxygen pressure and the amount of oxygen bound to hemoglobin. The results indicate that in pH 7.4 phosphate buffered saline the maximum rate of oxidation occurs in the region of 7 mM Hg with a rate slightly greater than 1%/hr. In the absence of oxygen as well as at atmospheric oxygen pressure a negligible rate of oxidation which is at least an order of magnitude slower, is observed. Our analysis indicates that hemoglobin with oxygen bound to three of the four subunits is the primary species responsible for the oxidation. Fully oxygenated hemoglobin is essentially not susceptible to oxidation while the rate for oxidation of hemoglobin with less than three oxygens bound is at least an order of magnitude slower than for the triligated species.

Erythrocytes. Erythrocytes contain enzyme systems for reducing oxidized hemoglobin, which are not thought to directly involve oxygen. We therefore expected erythrocytes to be oxidized to a lesser extent than hemoglobin. Furthermore, consistent with the reduced oxygen affinity for hemoglobin in erythrocytes, it was expected that the maximum rate of oxidation would be shifted to higher pressures. Our results instead, indicate a significant shift to lower oxygen pressures with the maximal rate of oxidation occurring in the very initial stages of oxygen binding. Furthermore, the level of oxidation under these hypoxic conditions are not appreciably reduced relative to that for purified hemoglobin. These results indicate that additional factors contribute to the oxidative stress produced in erythrocytes under hypoxic conditions. Studies are currently underway to delineate these factors.

Oxygen Binding to Hemoglobin. Detailed understanding of the coordination of ligands to hemoglobin is necessary to explain the role of hemoglobin in regulating effective transport of oxygen. Although conformational changes which dramatically alter oxygen affinity, occur during the binding of the four oxygen molecules to hemoglobin, essentially no information is available on the changes in the coordination of oxygen with hemoglobin at different stages in the binding process.

We have found that the autoxidation of hemoglobin is particularly sensitive to the nature of the oxygen coordination (see above). By studying the autoxidation as a function of the oxygenation of hemoglobin we have been able to delineate an intermediate state of hemoglobin with three oxygen molecules bound which is particularly sensitive to autoxidation. The oxygen coordination in this state must be distinct from oxygen bound to hemoglobin in the deoxy conformation at lower oxygen pressures and to the oxyhemoglobin conformation at higher oxygen pressures.

Further information regarding these partially liganded hemoglobins can be obtained by the use of hybrids which only bind oxygen to some of the subunits. Ni substituted hemoglobins are particularly valuable in this respect. The Ni subunit is stable and does not bind oxygen and remains in the deoxygenated conformation even in the presence of excess oxygen. We have fully analyzed the electron paramagnetic resonance of Ni substituted heme proteins and are now in a position to detect subtle perturbations at the metal center of the unliganded subunits. These changes can be followed at the same time that the rate of autoxidation is used to probe the oxygenated subunits.

Spectroscopic Identification of Distinct Classes of Cytochrome P-450. The cytochrome P-450s are an important class of heme proteins which utilize oxygen to metabolize lipid soluble substances. In collaboration with Fred Friedman of the Laboratory of Molecular Carcinogenesis, NCI, we have previously found that, although most of the cytochrome P-450 testosterone activities decrease with age, the activity of the cytochrome P-450 isoenzyme associated with the hydroxylation of testosterone at the 7 α position surprisingly increases with age.

We have now been able to spectroscopically identify three classes of cytochrome P-450s, two of which interact with testosterone. One of these classes undergoes a shift to a high spin state when bound to testosterone and is present to a greater extent in young rats. The second remains in a perturbed low spin state after binding to testosterone and is actually present to a greater extent in old rats. This class of cytochrome P-450 is presumably associated with the 7 α hybridization.

MACROMOLECULAR CHEMISTRY SECTION

Cyclodextrins. Cyclodextrins seem to be compounds eminently suitable for this purpose. That this approach is feasible is illustrated by oral testosterone supplementation, a method developed in the Section. The objective of the work on catecholamine receptors is to produce new models for the study of diseases of that system, a process which may eventually help in the development of new therapies.

2-Hydroxypropyl- β -cyclodextrin was prepared for the first time twenty years ago. Nevertheless, the compound remained dormant until its usefulness for biomedical purposes was discovered (Pitha J and Pitha J, J. Pharm. Sci. 1985;74:987-990). Currently the compound is produced in Japan, Hungary, Germany, and the United States in 20 kg lots, its toxicology has been investigated in detail, and was used, as a component of IND (FDA approved) in Great Britain in patients. These developments prompted us to extend our previous structural studies of this compound (Pitha J, Milecki J, Fales HM, Pannell L, Uekama K, Int. J. Pharm. 1986;29:73-82). Locally this project involved Dr. Irie and Dr. H.M. Fales, a mass spectrometry expert at NHLBI. Furthermore, we were aided in these efforts by Kaken Pharmaceutical Co., Ltd (Tokyo, Japan) who sponsored their employee (Mr. Fukunaga) to work with us for two years. These studies (Pitha J, Szabo L, Fales HM, Carbohydr. Res. 1987;168:191-198; Irie T et al., manuscript in preparation) demonstrated that (a) there are only small differences in reactivity of α -, β -, or γ -cyclodextrins with epoxides in aqueous alkali, (b) there is a good correlation between the ratio of the reactants used and the final average degree of substitution, and (c) the distribution of substitution is not random: there is a definitive tendency for the growth of short epoxide chains.

The acceptance of 2-hydroxypropyl- β -cyclodextrin by the biomedical and pharmaceutical community made us re-examine our theories on the importance of the amorphous state and to look for an alternative to the crystalline state. Consequently, we investigated the usefulness of unmodified γ -cyclodextrin and found it somewhat inferior to amorphous complexes but still useful (Pitha J, Anaissie EJ, Uekama K, J. Pharm. Sci. 1987;76:788-90).

Testosterone. Perhaps our most significant finding this year was made by an extramural collaborator, Dr. George T. Taylor. Dr. Taylor evaluated the testosterone:2-hydroxypropyl- β -cyclodextrin preparation developed in the Section, a preparation which may be used to obtain a

"burst-like" increase and fall in circulatory concentration of this hormone. Working with senescent rats, Dr. Taylor found that (a) this new preparation improves the "maleness" behavior pattern, (b) the prostate enlargement is much less than with the currently used testosterone ester preparations, and (c) not only does the cyclodextrin preparation not inhibit spermatogenesis, as testosterone ester preparations do, but stimulates the process.

Alpha-one Adrenoceptors. We continued to study the previously prepared alkylating derivative of prazosin *in vitro*. The data confirms the existence of sub-types of the alpha-one adrenoceptor, which was only recently (1987) described by Dr. K.P. Minneman and his colleagues. In collaboration with Dr. M.T. Piasecik (Univ. of Kentucky), Dr. Kusiak has started the evaluation of alkylating prazosin on the vascular system (aorta) using the organ bath method. Extending the chemical work in the field of prazosin analogs, Dr. Chida synthesized several compounds closely related to the alkylating prazosin.

MOLECULAR PHYSIOLOGY AND GENETICS SECTION

Estrogen action during aging. We have determined that loss of estrogen receptors from aged rat uterus cannot be the consequence of cell loss in endometrium, endometrial stroma and serosal epithelium. Computerized imaging of autoradiographic analysis of specific ³H-estradiol binding reveals that no significant cell loss occurs during aging in any uterine region, with only myometrium even showing a trend toward possible cell loss in the absence of receptor loss per cell.

Age-related increases in basal and estrogen stimulated pituitary prolactin production and decreases in luteinizing hormone (LH) production appear to occur through different mechanisms. In the former case mRNA levels are only slightly increased with age, not nearly enough to account for the 2-3 fold increase in prolactin levels. In the latter, mRNA and LH levels are comparably reduced (50-70%).

Estrogenic induction of apolipoprotein A1 is reduced by more than 50% in primary hepatocytes cultured from senescent rats. Such impairment may be related to an increased susceptibility to cardiovascular disease in situations (such as senescence) in which apolipoprotein A1 regulation of HDL levels is compromised.

Our previous studies suggested that impaired estrogenic and androgenic regulation of macrophage function is at least partially responsible for slower cutaneous wound healing in aged rodents. We have now demonstrated that wound healing rates can be increased by application of peritoneal macrophages to such wounds. In fact, senescent mice can be essentially restored to healing rates of young animals by this manipulation. Macrophages obtained from young mice appear to be slightly more efficient than those from older donors.

Regulation of calcium mobilization during aging. We have determined that no changes in parotid acinar cell IP_3 receptor concentrations or affinity occur during aging. Instead, preliminary results suggest that age-associated reductions in calcium dependent alpha-adrenergic stimulated secretory function may be due in part to decreased ability to take in extracellular calcium. It also appears possible that intracellular "second messengers" other than IP_3 may mediate these responses. For example, arachidonic acid can directly stimulate calcium mobilization in parotid cells, and possible age differences in arachidonate metabolism might help to explain differential age changes in adrenergic and cholinergic regulation of secretion.

As stated above, one aspect of cholinergic regulation of motor function proceeds through calcium dependent stimulation of striatal dopamine release. This effect is decreased with age, but can be restored to young adult levels in striatal slices by administration of A23187. Thus, as in many other calcium dependent systems, age-related functional decline can be at least partially reversed by appropriate manipulation of calcium fluxes. When IP_3 is administered directly, older striata exhibit a slight but nonsignificant reduction in dopamine release. As in the parotid, we have observed no changes with age in striatal IP_3 receptors. Also, as in the parotid, it appears that arachidonic acid may serve as another intracellular mediator of calcium release.

Since age changes in calcium mobilization also appear to account for decreased LH releasing hormone stimulation of pituitary LH secretion with age, we are attempting to elucidate the molecular mechanisms responsible for this impairment. To date, direct attempts to stimulate LH release by IP_3 have been unsuccessful. However, a synergistic effect of phorbol esters and other calcium mobilizing agents suggests that protein kinase C may somehow be involved in the process. Moreover a combination of A23187 and phorbol myristic acid administration can increase LH release from old rat pituitary cells to levels comparable to young. This represents still another case of functional restoration by manipulation of calcium mobilization.

Effects of Aging on Sensori-Motor Performance in Rodents. As a model of age-related decline in motor performance, we have been investigating in mice the effects of various pharmacologic manipulations of the nigro-striatal dopaminergic system in collaboration with Drs. Joseph, Roth, and Gupta. Young (6-mo) C57BL/6J mice treated with the selective nigral dopaminergic neurotoxin, n-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP), show symptoms of motor dysfunction similar to senescent mice. Further work will determine if MPTP effects are exaggerated in aged mice in both behavioral and morphologic parameters.

Assuming that loss of function in the nigrostriatal system is responsible in part for age-related decline in motor performance, we are also investigating possible mechanisms for this decline. MPTP is thought to exert its toxic effects through a mechanism of oxygen radicals produced when the catecholaminergic degradative enzyme,

monoamine oxidase-B, acts on the compound. The toxic effects of MPTP can be eliminated with sufficient doses of monoamine oxidase-B inhibitors, such as deprenyl. We have administered deprenyl in the drinking water of 18-mo old male C57BL/6J mice and observed these mice in a battery of motor tests at 24 mo of age. No evidence of toxicity was noted as the treated mice exhibited normal fluid intake and body weights. Although the study is incomplete, some evidence is emerging that age-related decline in selected motor tests, tightrope and rotorod, was less in deprenyl-treated mice compared to controls. This study will be completed with additional behavioral testing and neurochemical and neuroanatomical assessments of the nigrostriatal dopaminergic system.

Effects of Aging on Learning/Memory Function in Rodents. Continued research has demonstrated the importance of the septo-hippocampal cholinergic system for efficient performance in our 14-unit T-maze to suggest that defects in this system may underlie the age-related impairment observed. Lesion damage to hippocampal pyramidal cells (using trimethyl tin injections) and to the medial septal nucleus (using electrolytic lesions) that provides cholinergic innervation to the hippocampus increase error performance in young (3-4 mo) male F-344 rats similar to that previously observed with scopolamine-treated (muscarinic antagonist) and fimbria-fornix (a major hippocampal pathway) lesions in young rats. These latter observations have also now been replicated in the newly developed detour maze in collaboration with Dr. Bresnahan. Scopolamine treatment in well-trained rats produced increased error performance in young rats with no effects on other aspects of performance. When these rats were subjected to fimbria-fornix lesions, increased error performance was also recorded. These observations paralleled the age-related increase in error performance also observed in this maze.

The role of the septo-hippocampal cholinergic system has been made more exclusive by results of experiments that manipulated levels of forebrain noradrenaline (NA). In collaboration with Dr. Wenk, we found that treatment with the neurotoxin, N-chloroethyl-N-ethyl-2-bromobenzylamine (DSP-5), resulted in severely depleted (80%) levels of forebrain NA in young (3-4 mo) male F-344 rats but had no effect on learning or retention performance in these animals in the 14-unit T-maze. In addition, when provided a gustatory neophobia test, which is a behavioral assay of the integrity of the forebrain NA system, aged (24-mo) male F-344 rats demonstrated increased neophobia (avoidance of novel gustatory stimulus, i.e., sucrose solution) compared to young (3-4 mo) counterparts; however, there was no correlation between this behavior and subsequent performance in the 14-unit T-maze. In this same series of studies, we also saw no evidence of a cholinergic-adrenergic interaction affecting performance in the 14-unit T-maze. Administration of relatively low doses of scopolamine to DSP-4 treated young (3-4 mo) male F-344 rats did not differentially impair their performance more than that of control rats receiving scopolamine only.

Environmental/Nutritional Modulation of Aging in Rodents. In collaboration with Drs. Bresnahan, McNeill, and Davis, we are investigating the behavioral and neurobiological effects of dietary restriction and environmental stimulation on aging male C57BL/6J mice.

The regimen of dietary restriction involves intermittent feeding (3/7 days per week) compared to ad libitum feeding from weaning. Environmental stimulation involves housing in either conventional cages (4 per cage) or in large group cages (32 per cage) or in large group cages containing a variety of objects changed three times weekly. Results continue to show that while dietary restriction significantly increases lifespan, environmental stimulation impacts negatively upon mean survival while not affecting maximum lifespan. In collaboration with Dr. Davis, we have since found that 20-mo old mice on dietary restriction since weaning have increased plasma insulin and decreased plasma glucagon but equivalent levels of plasma glucose compared to ad lib fed controls. This neuroendocrine profile may suggest increased metabolic efficiency of the restricted animals for metabolizing glucose. The activity of adrenal tyrosine hydroxylase was also increased in restricted mice compared to controls and this observation paralleled morphological evidence of increased glucogen and lipid deposition in liver compared to controls. However, we have analyzed mice only when all had received at least 24-hr access to food. Systematic study of these parameters during different feeding times is planned.

Effects of Fetal Neural Tissue Transplants on Behavioral Aging in Rodents. In collaboration with Drs. Talan, Bresnahan, and Gage, we are undertaking a large study to assess the behavioral and physiological effects of fetal hypothalamic grafts placed into the third cerebral ventricles of middle-aged (16-18 mo) and aged (26 mo) male C57BL/6J mouse hosts. Our initial experiments involve testing of 30-mo old mice that have received grafts at 26-mo of age. Control groups include grafts of neocortical tissue, pieces of fat or muscle, and operated and unoperated controls. Histological examination has verified that some survivors have viable grafts (adult-size neurons, minimal gliosis, interfaced to host tissue) when the hypothalamic transplant was made to the dorsal or ventral aspect of the third ventricle. The difference between the two treatments is that in the dorsal aspect of the ventricle, the graft can exert only distal influence possibly through the portal or ventricular system; whereas, with the ventrally placed graft, there is the greater possibility of direct neural contact with the target hypothalamus of the host. The behavioral and physiological battery includes open-field activity, tightrope test, rotorod test, water consumption, body temperature, oxygen consumption, cold tolerance, runwheel activity, and running speed test. Consistent with theories hypothesizing a decline in hypothalamic function as a mechanism of mammalian aging, the objective was to determine whether the hypothalamic grafts would restore or prevent further age-related decline compared to controls. When surviving hosts judged to have viable grafts in or out of the targeted locations were compared to control groups, little evidence of functional improvement was observed. In fact, further functional decline was often noted among these aged hosts in some tests. In addition, a much greater rate of mortality was observed among grafted mice compared to unoperated controls. The analysis of mice receiving grafts at 16-18 mo of age and tested at 24-mo has not been completed.

We are also utilizing the technology of fetal neural tissue grafting to assess the neurobiology of the age-related impairment in complex maze learning. Specifically, young male F-344 rats (3-4 mo) rats receive

electrolytic lesions to the fimbria-fornix, which will impair their maze performance compared to young controls. Different groups of lesioned rats receive plugs of fetal septum (E15-16 day old fetuses) into the lesion cavity or into the dorsal third ventricle. Other groups of young lesioned and intact aged rats (22-mo) receive injections of septal cellular suspensions directly into the hippocampus. These animals along with proper controls will undergo an extensive battery of motor and learning tests to determine the impact of the grafting procedure. Preliminary results now indicate that the grafts had little favorable impact upon performance in motor or learning tests.

Stability of Proper Gene Expression. Preliminary studies in our laboratory have found an age-dependent increase in expression of c-type retrovirus with age (MuLV and MMTV) in mice. We are continuing these studies by investigating possible age-dependent derepression of a number of oncogenes in various tissues of the C57BL/6J Mus musculus, wild-type Mus musculus, and Peromyscus leucopus. The oncogenic cDNA probes being used are N-myc, L-myc, C-myc, c-Ki-ras, and c-Ha-ras-1. Tissues are brain, liver, heart, kidney, intestine, liver and skin tissues. For N- and L-myc genes, a high expression is found in endogenous tissues, which decreases to background levels at later ages and remains low throughout the rest of the life span.

Measurement of oxidative DNA damage. In collaboration with Dr. Michael Simic and co-workers at NBS, we have been studying the possible age-dependent accumulation of oxidized nucleic acid components in the DNA of mice and primate species. We are also studying the feasibility of using the GC/MS technique for measuring oxidized nucleosides in urine. This technique now appears to be successful, and it is being used to determine if a correlation exists between urine output of a given oxidized nucleoside with the life span of different primate species. Our results to date indicate that the urinary output of thymidine glycol and 8-hydroxydeoxyguanosine per creatinine is least in human and increases as a function of a species decreasing life span.

Results in our laboratory using an improved method to digest the DNA samples now uniformly shows that normal endogenous levels of 8-OHdG per dG in DNA of liver steadily decreases as life span increases, with humans having the lowest level of 8-OHdG per dG content. The amount of 8-OHdG per amount of creatinine in urine was measured for species of differing life spans: human (100), chimpanzee (55), Rhesus (40), squirrel monkey (25), marmoset (20), tree shrew (15), Peromyscus leucopus (8), and Mus (3) (approx. life span in parentheses). In addition, we included elephant and cebus. This was done to determine if amounts found correlated with metabolic rate rather than life span. In this case, elephant would be expected to be very low and galago and cebus to be high. Results showed that the correlation fits life span - not metabolic rate.

Taken together, these results suggest that oxidative damage to DNA not only remains for longer periods of time in shorter-lived species but also has a higher turnover or repair rate as indicated by the high urine output of these oxidized nucleosides. Thus, the DNA in shorter-lived species may be both damaged at a higher rate and repaired at a higher

rate. This result leads to the new concept that, in spite of DNA not accumulating damage with age, high turnover rate nevertheless could be dangerous in promoting increased chromosomal rearrangements and other genomic perturbations contributing toward gene instability. Thus, prevention of damage rather than repair might be the preferred method to protect the integrity of the DNA. This result, if confirmed in later studies, could be of fundamental importance in understanding both the mechanisms of aging and of those processes governing aging rate.

NOTICE OF INTRAMURAL RESEARCH PROJECT

201 AG 00044-15 LCMB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effect of Metals and Proteins on Nucleic Acids, Information Transfer and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	Gunther L. Eichhorn	Chief, LCMB	IBS LCMB NIA
Others:	Richard B. Beal (EOD 2/1/88)	IRTA Fellow	IBS LCMB NIA
	James J. Butzow	Commissioned Officer	IBS LCMB NIA
	Peter P. Chuknyisky (EOD 5/1/87)	Sr. Staff Fellow	IBS LCMB NIA
	Patricia Clark	Research Chemist	IBS LCMB NIA
	Robert E. Kilkuskie (DOD 1/8/88)	NRC Res. Research Assoc.	IBS LCMB NIA
	Yong A. Shin	Research Chemist	IBS LCMB NIA

COOPERATING UNITS (if any) Johns Hopkins University (L. Liu, E. Freire, E. Moudrianakis, M. Beer); Max Planck Institute (M. Soumpasis); University of Oregon (C. Johnson); Wichita State University (R.P. Singhal); University of Western Ontario (S.J. Karlik); University of Toronto (U. DeBoni)

LAB/BRANCH

Laboratory of Cellular and Molecular Biology

SECTION

Inorganic Biochemistry Section

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

7.5

PROFESSIONAL:

5.5

OTHER:

2

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project focuses on the interaction of molecules concerned with genetic information transfer. A primary objective is to determine under what conditions metal ions are essential for information transfer, and under what conditions they impact on the information in such a way as to influence biological aging. Topics of interest are: (1) the effects of metal ions on the structure of nucleic acids, nucleoproteins and chromatin; (2) the mechanism of involvement of aluminum in Alzheimer's disease; (3) crosslinking of nucleic acid strands by metal ions; (4) the structure of the active site of RNA polymerase; (5) metal ions and cellular aging.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00113-5 LCMB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

In Vivo NMR Studies of Aging in Cells and Animals

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Gunther L. Eichhorn	Chief, LCMB	IBS LCMB NIA
Others:	Rajasekharan P. Pillai	Senior Staff Fellow	IBS LCMB NIA
	(DOD 07/01/88)		
	Richard B. Beal (EOD 02/01/88)	IRTA Fellow	IBS LCMB NIA

COOPERATING UNITS (if any)

Cardiovascular Section, Clinical Physiology Branch, National Institute on Aging;
Department of Radiology, Johns Hopkins University

LAB/BRANCH

Laboratory of Cellular and Molecular Biology

SECTION

Inorganic Biochemistry Section

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

0.8

PROFESSIONAL:

0.8

OTHER:

0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

NMR Spectroscopy is used to study the metabolic changes associated with exercise in the flexor muscle of the forearm of human volunteers. Isometric exercise at variable workloads as well as constant workload are carried out using a hand dynamometer which is interfaced to a personal computer and a display unit. Changes in phosphocreatine (PCr) and inorganic phosphate (P_i) as well as intracellular pH are monitored via ^{31}P NMR spectroscopy during the exercise. Age-related differences in these parameters during exercise will be studied in subjects of the BLSA using these protocols.

IRP-LCMB-70

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00047-18 LCMB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Structure-Function Relationships in Hemoglobin and Erythrocytes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	Joseph M. Rifkind	Chief, MDS	MDS LCMB NIA
Others:	Periannan Kuppusamy (DOD 11/10/87)	Visiting Fellow	MDS LCMB NIA
	Abraham Levy	Sr. Staff Fellow	MDS LCMB NIA
	Lu Zhang (EOD 11/08/86)	Visiting Fellow	MDS LCMB NIA

COOPERATING UNITS (if any) NIA/LCS/CFS (E. Lakatta); IR TD/NHLBI (R. Berger); LMC/NCI (F. Friedman); Indian Inst. of Technology, Madras, India (P.T. Manoharan); University of California - San Diego, La Jolla, CA (V.S. Sharma); University of Washington, Seattle, WA (J.W. Heinecke).

LAB/BRANCH

Laboratory of Cellular and Molecular Biology

SECTION

Molecular Dynamics Section

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

4.11

PROFESSIONAL:

3.11

OTHER:

1

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project focuses on the mechanisms involved in regulating the binding of oxygen to hemoglobin and the transport of oxygen to the tissues. Emphasis is placed on ways in which these functions are impaired and change with age. These studies have focused on the oxidation of hemoglobin, which produces non-function hemoglobin and the simultaneous release of oxyradicals. The enhancement of these oxidative processes under hypoxic conditions is being explored as a possible source of tissue and organ damage, which would be exacerbated during aging. Studies are also included which are directed at the stability of the entire erythrocyte and the erythrocyte membrane.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00046-18 LCMB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Medicinal Chemistry Applied to Problems Prominent in Senescence

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Josef Pitha	Section Chief	MCS LCMB NIA
Others:	John Kusiak	Research Chemist	MCS LCMB NIA
	Yasuhiro Chida EOD 4-1-86	Visiting Fellow	MCS LCMB NIA
	Tetsumi Irie DOD 4-30-88	Visiting Fellow	MCS LCMB NIA
	C. Trinadha Rao EOD 10-27-87	Visiting Fellow	MCS LCMB NIA

COOPERATING UNITS (if any) Univ. Florida, Gainesville, FL (Dr. Baker); NHLBI, NIH, Bethesda, MD (Dr. Fales); Univ. Missouri, St. Louis, MO (Dr. Taylor); Kaken Pharmaceutical Co., Ltd., Tokyo, Japan (Mr. Fukunaga); Kumamoto Univ., Kumamoto, Japan (Prof. Uekama); Univ. Kentucky, Lexington, KY (Dr. Piascik)

LAB/BRANCH

Laboratory of Cellular and Molecular Biology

SECTION

Macromolecular Chemistry Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland

TOTAL MAN-YEARS:

5.50

PROFESSIONAL:

4.50

OTHER:

1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Amorphous derivatives of cyclodextrins, compounds which (a) combine the advantages of host-guest complexation of drug with the advantages of the conversion of drug into a stable amorphous state, (b) have low toxicity, (c) can be fully characterized, and (d) were developed in the Section, have started to come of age. These compounds are currently produced in several countries and have already been used in one clinical trial.

IRP-LCMB-72

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG 00301-5 LCMB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less Title must fit on one line between the borders)

Regulation of Physiological

Functions During Aging: I. Hormone and Neurotransmitter Action.

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal investigator) (Name, title, laboratory, and institute affiliation)

PI: G.S. Roth, Chief, Molecular Physiology and Genetic Section, LCMB, NIA

Others:

T. Maki

J. Joseph (EOD 4/88)

K. Kochman (DOD 12/87)

Z. Han

B. Baum

M. Blackman

COOPERATING UNITS (if any)

Patient Care Branch, National Institute of Dental Research; Clinical Physiology Branch, NIA Armed Forces Radiobiological Research Institute; Unit of Lab. Animal Medicine, U. of Mich.

LAB/BRANCH

Gerontology Research Center,

SECTION

Molecular Physiology and Genetics Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS

4.5

PROFESSIONAL

4.0

OTHER

0.5

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type Do not exceed the space provided)

This project is mainly involved in elucidating those mechanisms by which the ability of hormones and neurotransmitters to regulate physiological functions is altered during aging.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00302-5 LCMB

PERIOD COVERED October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Functions During Aging: ~~Regulation of Physiological~~ II. Behavioral BiologyPRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)
PI: Donald K. Ingram, Research Psychologist MPGS, LCMB, NIA

Others:

C. Barnes	E. Bresnahan	B. Davis	G. Roth
F. Gage	H. Kametani	S. Kobayashi	M. Talan
J. Joseph	T. McNeill	D. Olton	
M. Gupta	G. Wenk	E. Spangler	

COOPERATING UNITS (if any)
Dept. Psychology, Johns Hopkins U., (D. Olton, C. Wenk); Essex Community College, (E. Bresnahan); Neuroanatomy Lab U. Rochester Sch. Med. (T. McNeill, B. Davis); F. Gage (U. C. San Diego, Sch. Med.) U. Louisville Sch. of Med. (M. Gupta) U. of Colorado (C. Barnes)

LAB/BRANCH Gerontology Research Center,

SECTION Molecular Physiology and Genetics Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS: 5.8	PROFESSIONAL: 3.5	OTHER: 2.3
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CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of this project is to assess the effects of aging at a behavioral level of analysis in animal models, to identify neurobiological mechanisms associated with these effects, and to test interventions which might alter age-related performance decrements. Rodent models are tested in a battery of sensori-motor and learning/memory tasks. Neurochemical assays are conducted to determine neurobiological correlates of functional losses. Interventions include dietary restriction, environmental enrichment, various pharmacologic treatments, and neural tissue grafting. Multiple genotypes are examined to determine possible genetic involvement in the pattern of age-related behavioral impairment.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00303-5 LCMB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Regulation of Physiological Functions During Aging: III Gene Expression and the Biology of Human Longevity

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)
PI: Richard G. Cutler, Research Chemist, LCMB, GRC, NIA

Other:

D. K. Ingram
I. Semsei
M. Simic
D. Bergtold
A. Ayala

G. Roth
H. Alessio
J. D. Gearhart
A. Brower
A. Brown

S. Ma
J. Vijg
R. Morgan
A. S. Khan
A. H. Goldfarb

COOPERATING UNITS (if any)

NIH, NIAID (A. Khan); NBS (M. Simic, D. Brower); Bergtold, M. Kyoto University (T. Ono); TNO (J. Vijg, A. Brower); J.D. Gearhart, M. L. Oster-Granite, R. Morgan, A. Brown.

LAB/BRANCH

Gerontology Research Center

SECTION

Molecular Physiology and Genetics Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

2.2

PROFESSIONAL:

2.0

OTHER:

0.2

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The long-term objective of our research project is to contribute towards an understanding of the genetic and biochemical basis determining the unusually long life span of humans as compared to other mammalian species. Our research program is currently focused on testing the hypothesis that aging may be a result of improper gene regulation (dysdifferentiation) and lifespan a result of a relatively few mechanisms acting to stabilize proper gene regulation (longevity determinants). Using Northern and slot-blot DNA hybridization techniques, a tissue- and age-dependent change in expression was found in endogenous retrovirus genes of both human and mouse tissues. Particularly striking has been the age-dependent increase in expression of the endogenous retroviral envelope genes and c-myc oncogenes in human kidney tissue and of the MuLV retroviral genes (full length and endogenous specific LTR region) and the L-, N- and c-myc family of genes in mouse kidney tissues. A normal mutational load of oxidative DNA damage (8-hydroxydeoxyguanosine and thymidine glycol) in liver of rodent and primate species has been found, which decreases slightly with age.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG-00304-2 LCMB

PERIOD COVERED October 1, 1987 to September 30, 1988

Regulation of Physiological

TITLE OF PROJECT (30 characters or less. Title must fit on one line between the borders.) Functions During Aging: IV.
Assessment of Primate Aging: Effects of Caloric Modification

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI's	G. S. Roth,	Chief, MPGS	LCMB, NIA
	D. K. Ingram,	Research Psychologist, MPGS	LCMB, NIA
	R. G. Cutler,	Research Chemist, MPGS	LCMB, NIA

Others:	R. Weindruch	D. Renquist,	M. April,	J. Knapka,	J. Tobin,
	S. Sherman,	M. Blackman,	M. Talan,	W. Ershler,	W. Stone,
	W. Wood	H. Armbrrecht	R. Strong	J. Conway	D. Danon

COOPERATING UNITS (if any)

Dept. of Med. Univ. of Wisc. Madison, WI
Dept. of Biol. Trinity Univ., San Antonio, TX

LAB/BRANCH

Gerontology Research Center,

SECTION

Molecular Physiology and Genetics Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

4.0

PROFESSIONAL:

2.0

OTHER:

2.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects	☐ (b) Human tissues	☐ (c) Neither
☐ (a1) Minors		
☐ (a2) Interviews		

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is attempting to determine whether caloric modification of the diets of Rhesus and squirrel monkeys can affect aging rate as assessed by various physiological, biochemical and behavioral indices.

ANNUAL REPORT OF THE LABORATORY OF CLINICAL PHYSIOLOGY
NATIONAL INSTITUTE ON AGING

The Laboratory of Clinical Physiology (LCP) is comprised of four sections -- Clinical Immunology, Endocrinology, Metabolism and Applied Physiology. The research approaches range from the more basic aspects of physiology, including molecular genetics and cell culture, to study of aging processes in experimental animals, to investigation of physiological processes in man. The human studies rely heavily on the Baltimore Longitudinal Study of Aging (BLSA) population of men and women with supplementation by special groups of individuals with characteristics which make them especially valuable for study. Thus, selected groups of middle-aged and elderly subjects who are obese or who are remarkably physically active (master's athletes) are also under study. In addition, elderly patients who are chronically hospitalized at the Francis Scott Key Medical Center (FSKMC) provide an important group of patients for studies in research geriatric medicine. While a great deal of inter-section and inter-laboratory collaboration occurs, for convenience, the activities of the Laboratory will be reported by Section.

Clinical Immunology Section

The Clinical Immunology Section conducts research on the various pathways that are involved with the control of the immune response. Cell free factors, cellular interactions, activation pathways, endocrine and neuroendocrine hormones, nutrition, trace metals, pathogens, and vitamins all can influence the type and degree of any immune response. The modulation of membrane receptors, the synthesis of receptors and the role of the interleukins are of particular interest. The effects of age on each modulating factor and the contribution of aging to changes in immune function are central to the goals of the research in the Section.

Research highlights of the past year were:

- o Resting T lymphocytes prepared from mice at least 24 months of age that are responsive to the mitogen Concanavalin A have the same quantity and quality of IL-2 receptors as similarly prepared cells from young mice. However, there is a significant sub-population of cells contained within the G0 T lymphocytes prepared from old mice which are unable to express detectable high affinity IL-2 receptors in response to mitogenic activation. This unresponsiveness is related to a deficiency in a transmembrane signaling mechanism in which protein kinase C is involved since phorbol diesters, nonspecific protein kinase C activators, induce the identical expression of IL-2 receptors as detected by ligand binding to T lymphocytes from both young and old mice. Although phorbol diesters by-pass the physiological pathway involved in the expression of IL-2 receptors, such receptors are not biologically functional. By limiting dilution analysis the size of the population of G0 T cells from old mice unable to express high affinity IL-2 receptors after mitogenic activation is estimated at 50-70% of the Thy 1.2 positive lymphocytes.

- o Cytochalasin B (CB) and cytochalasin E (CE) interact with the mitogen, Concanavalin A (Con A), and the lymphokine, IL2, in activation and signal transduction in splenocytes and G0 T cells from young and old mice. Both cytochalasins synergize with Con A at very low concentrations, presumably by interacting with high affinity binding sites. No age-related differences in mitogenesis were observed with low concentrations of CB and CE either alone or in synergy with Con A.
- o Higher concentrations of CB combined with mitogenic concentrations of Con A and IL2, inhibited tritiated thymidine incorporation in all G0 T cells due to inhibition of glucose transport. Higher concentrations of CE, which do not inhibit glucose transport, plus Con A and IL2 had differential effects on thymidine incorporation by G0 T cells from young and senescent mice: it inhibited the young and enhanced the old. CE binding to low affinity binding sites, actin, in the cytosol causes depolymerization of actin. This suggests that age-related changes in the state of polymerization of actin in microfilaments contribute to the decline in T lymphocyte function with age. In addition, CE bound to low affinity sites interacted with IL2 alone to drive G0 T cells from old but not young mice into the cell cycle.
- o There are several fundamental observations about T cells from aged humans. Neither defective interleukin 2 synthesis or a lack of high affinity IL2 receptors are the basis for the well documented proliferative defect of T cells from aged persons. T cells from elderly individuals are not genetically defective in their ability to make IL2 or IL2R mRNA. Studies with PHA and anti-CD3 indicate that there is a problem with signal transduction from the cell membrane to the nucleus since cells directly activated with PMA/A23187 do not display any defects in IL2 or IL2R synthesis and have nearly identical numbers of high affinity IL2R by radioligand studies. Recent work appears to indicate that different activation stimuli may have different effects on the production of or the interaction between the p55 and p70-75 (Ca and Cb) subunits of the IL2R and that there may be a functional deficit in the high affinity receptor in cells from elderly individuals.
- o Work with Alzheimer's patients' brain specimens has shown no evidence of the presence of unusual levels of common viral genome. There is no excessive accumulation of mRNA for tubulin, even though there is an accumulation of tubulin in the brain tissue. There is no duplication of the superoxide dysmutase gene in Alzheimer's tissue and no increase in the mRNA for SOD. There does appear to be a deficit in gene expression for neurofilaments in tissue from Alzheimer's patients.

Applied Physiology Section

The Applied Physiology Section is concerned with studying the relationship of levels, and rates of changes in levels, of performance of physiologic and non physiologic variables in health and disease. The two major areas of interest are the study of bone, both osteoporosis and osteoarthritis, and a new effort on strength assessment. The latter effort was initiated because of the apparent interrelationship of strength, and the physical stresses of muscle, on bone resorption and apposition. In addition, the concept of fitness has focused on aerobic conditioning (VO₂ max) and its possible relationship to metabolic and cardiovascular diseases. A similar effort is necessary to define the role of muscle strength with age on some of the functional and disease changes which occur. Other areas of interest in the section include ongoing studies on renal and glucose physiology; studies of genetic markers in an effort to understand the etiology of diseases with late onset, such as Amyotrophic Lateral Sclerosis Parkinsonism-Dementia, Alzheimer's disease, osteoporosis, osteoarthritis, and breast cancer; and cross cultural studies of genetic and non genetic variables in an effort to obtain a better understanding of the factors affecting normative aging processes.

Research highlights of the past year were:

- o Digital and palmar dermatoglyphics were examined in 58 men and women with dementia of the Alzheimer's type (DAT) and in 112 matched controls; no significant differences were found and there was no similarity in the patterns of DAT and Down's syndrome patients.
- o However, dermatoglyphic patterns of women with breast cancer in the United States and in Finland both showed statistically significant differences from patterns in control subjects.
- o Photon absorptiometry in 3 sites in the proximal femur and in the forearm, lumbar spine, and second metacarpal bone showed that correlations of bone density among these sites were statistically significant, the strength of the associations were generally weak. Estimations of bone mineral content must be carried out at that site; conclusions based upon estimates at distant sites are not useful.
- o Decline in 24-hour creatinine clearance is not related to decline in either resting or exercise cardiac performance in BLSA subjects carefully screened for the presence of coronary artery disease. In that sense, the "rates of aging" of these two systems are independent. Decline in renal function is apparently an endogenous renal process.

with chronologic age. Primary contributors to the decline in tolerance in stepwise multivariate regression analysis in a population of healthy individuals, were obesity, fat distribution, and age. Effects of physical activity and fitness were exerted through influence on body weight; no further independent contribution was made when weight was taken into account. Age remains as a determinant unexplained by the associated age-related variables of disease, medications, fatness, fitness, and fat distribution pattern.

- o Analysis of dietary intakes in the BLSA population over a 20 year span (1960s to current time) showed that the longitudinal changes which the subjects voluntarily initiated between the 1960s and 1970s continued at a comparable pace into the 1980s. Notable changes included a further decrease in calories from fat and increased in P/S ratio and in fiber intake. These changes occurred in young, middle-aged, and elderly individuals.
- o Collaborative studies with NCI scientists provided favorable conclusions for the possibility of using retrospective dietary histories in the epidemiologic search for dietary causative factors for the major diseases of Americans (cancer and heart disease). The study took advantage of the fact that BLSA men provided 7-day dietary diaries in 1971-75. The same men then provided dietary information on the same period of time by current self-administered questionnaires or by personal interview. The questionnaires will provide less satisfactory data unless preceded by personal instruction and call-backs. The interview provided information remarkably consistent with the information originally provided.

Metabolism Section

The underlying objective of the Metabolism Section (MS) is to gain an understanding of the metabolic complexities associated with aging. In the simplest terms, "primary" biological processes of aging are associated with a wide variety of "secondary" processes. The latter processes include such variables as inactivity, diet, body composition changes (lean body mass, obesity, and fat distribution pattern), and the effects of multiple disease processes and medications. On the one hand, it is our objective to dissect away the secondary effects so that true biological aging processes in man can be understood. On the other hand, the secondary processes may well prove to be of equal or greater importance in the determination of the overall picture of the aging human being. An understanding of these effects and of their relationship to primary aging processes is fundamental for the planning of rational processes to maintain health during aging and to prevent the diseases and infirmities so characteristic of the elderly.

Specifically, the research objectives of the Metabolism Section are: (1) to describe age differences and age changes in metabolic variables; (2) to determine biological mechanisms underlying those age effects; (3) to assess the impact of those age effects on other variables, on disease development, and on mortality; and (4) to define normative standards as influenced by age. The major metabolic variables include glucose homeostatic factors, insulin secretion and sensitivity to insulin, body composition including lean body mass, obesity, and fat distribution, acute effects of physical activity, long-term effects of physical fitness, and dietary variables, serum lipids, and adipose tissue metabolism.

Research highlights in the past year were:

- o Cigarette smokers in the BLSA population had a more harmful pattern of fat distribution (waist hip ratio) than non-smokers. Despite the expected loss in weight in those who initiated smoking while under study, the WHR increased - a paradoxical and harmful effect. On the other hand those who quit smoking did, on average, gain weight, but the predicted increase in WHR anticipated with gain in weight did not occur. The decision to initiate or to restart smoking or to continue smoking in order to control body weight is doubly harmful: the direct effects of smoking will be re-enforced by a more dangerous pattern of distribution of body fat.
- o Variables contributing to the decline in glucose tolerance accompanying aging have been examined in the BLSA male and female volunteers. Obesity (assessed by several techniques), pattern of distribution of body fat, physical activity habits (assessed by questionnaire), physical fitness (assessed by determining V02max on treadmill exercise) were analyzed along

- o In a large group of men ages 35-88, studied prospectively, prevailing serum levels of estradiol and testosterone were not risk factors for development of coronary atherosclerotic heart disease. However, low serum levels of estradiol and high levels of total cholesterol appear to be significant risk factors in younger (but not older) men. By contrast, hypertension was a significant risk factor in older (but not younger) men.
- o Increases in both in vivo and in vitro secretion of prolactin (PRL), and decreases in secretion of LH and FSH, occur often in old male and female rats. Using cDNA probes for rat PRL and rat LH-Beta subunit, we found stable levels of PRL in RNA to be unaltered, whereas levels of LH-Beta in RNA are reduced, in both tissues and pituitary cells from old female rats. The apparent failure to increase PRL gene expression in old rats, despite enhanced PRL secretion, is a novel finding, the mechanism of which promises insights into the aging process.

Endocrinology Section

The Endocrinology Section is engaged in studies of the mechanisms by which aging affects the secretion and action of hormones in animals, tissue culture, and human subjects. Current work involves clinical and basic investigations in these areas. Also studied is the interrelationship of aging to clinical disease, especially chronic illness. Of special note is work related to anterior pituitary hormone and/or sex steroid secretory physiology. The clinical research includes studies of (a) effects of aging and sex steroid hormones on the dynamics of pituitary growth hormone secretory physiology in men and women (b) the interrelationships between circulating levels of sex steroids and various coronary artery disease risk factors in men (c) the effects of administration of varying doses of parenteral estrogen (replacement therapy) on hormonal parameters related to bone metabolism (and osteoporosis risk) in postmenopausal women of different ages, and (d) relationships among body composition, body fat distribution, lipid and glucose metabolism and sex steroid hormone secretion in men and women of different ages. Basic investigations utilize hypothalamic and anterior pituitary tissues and/or cells from aged rodents to examine the cell physiological, biochemical, and molecular genetic mechanisms underlying reproductive senescence.

Current experimental work emphasizes biochemical studies of age-related alterations of hormone action which are mediated at the level of hormone-receptor interactions in the cell outer membrane but also includes studies of hormone action at the intracellular level. Hormone-sensitive fat cells are being studied in cell culture in order to develop a model system for analysis of the mechanisms involved in age-related alterations of hormonal responsiveness. Other aspects of the work with cultured cells relates to studies of hormonal control of differentiation and cell growth and is of special relevance to research in obesity.

Research highlights of the past year were:

- o Fat cells in culture secrete a differentiation factor which promotes the adipose conversion of islet-derived cells, highly committed adipocyte precursors. This factor, a regulator of adipocyte development, is of potential importance for the study of obesity.
- o A novel low affinity Beta-adrenergic receptor is present during the development of preadipocytes. This receptor has now been shown to be larger than the Beta-adrenergic receptor of mature adipocytes. This finding indicates that the biosynthesis of the Beta-adrenergic receptor probably proceeds through a form which contains an additional segment in a manner analogous to the synthesis of some large, polypeptide hormones.

- o In families with histories of neurofibromatosis there is a linkage between NF and chromosome 17 areas detected by the cDNA probes EW206, EW207, and D1721. These probes can be used for prenatal diagnostic procedures as well as detection of the NF carrier state.
- o The cerebrospinal fluid from multiple sclerosis patients contains high levels of the soluble IL2 receptor which indicates an immunologic mechanism in the pathogenesis of this disease.
- o Prolactin can inhibit mature T lymphocyte activation. Normal lymphocytes in the peripheral blood have receptors for prolactin and have prolactin on their membranes. This may be an important control mechanism. Prolactin effects vary as to the age and gender of the lymphocyte donor.
- o Burn patients have a marked drop in the numbers of circulating T cells with a subsequent appearance of immature forms of T cells during the recovery period. This pattern is not seen even in older patients and suggests that thymic function is deficient in individuals at 40 yr of age and older.
- o The transcription of the gene for IL-2 can be selectively inhibited by the vanadate ion. Vanadate does not inhibit the transcription of the IL-2R gene. Therefore activation pathways exist for each of these genes and they are not coupled.
- o An in vitro test for a cellular response to the HIV GP120 antigen has been developed and may be useful for measuring immunity to the vaccine antigen.
- o The drug, amyl nitrate, is frequently abused by the homosexual community. Since that group is at risk for AIDS and Kaposi Sarcoma, its effect on immune function was assayed. Amyl nitrate causes a short term depression of NK function, and T lymphocyte numbers, and a rebound phenomenon in which lymphocytes are activated, B cells secrete higher levels of Ig and T lymphocytes are increased in peripheral blood. Immunostimulation may increase the risk of and extent of an HIV infection.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00093-16-LCP

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cellular Basis of Regulation of the Humoral Immune Response

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	A. A. Nordin	Research Chemist	LCP, NIA
Others:	J. J. Proust	NIH Special Volunteer	LCP, NIA
	M. A. Buchholz	Biologist	LCP, NIA
	F. J. Chrest	Biologist	LCP, NIA
	R. S. Pyle	Bio Lab Tech	LCP, NIA

COOPERATING UNITS (if any)

C. Filburn, LBC, NIA, D. Kittur, Dept. Surgery, Johns Hopkins University,
J. Shaper, Oncology, Johns Hopkins University, Baltimore, MD.

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Clinical Immunology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore Maryland 21224

TOTAL MAN-YEARS:

3.2

PROFESSIONAL:

2.0

OTHER:

1.2

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Murine Go T-cells from young (2-4 mo.) and old (24-27 mo.) animals do not express detectable levels of high or low affinity IL-2 receptors. After 40 hrs. of incubation with either PMA or Con A together with recombinant IL-2, the number and affinity of IL-2 receptors is indistinguishable by age. However, the number of cells surviving the incubation period is remarkably lower in cultures containing T-cells from the older mice. Similarly prepared Go T cells when incubated with Con A for 8 or 16 hrs. expressed high affinity IL-2 receptors in an age-related fashion. Cells derived from old animals failed to develop high affinity IL-2 receptors as detected by radioligand binding assays. Cells derived from young animals expressed detectable levels of high affinity IL-2 receptors 8 hrs. after incubation with Con A and by 16 hrs. the number of these receptors increased significantly. Similar studies performed with phorbol diesters in place of Con A showed no age-associated difference in the expression of high or low affinity IL-2 receptors as detected by radioligand binding. The high affinity IL-2 receptors induced by phorbol diester fail to deliver a proliferative signal under physiological conditions. Extremely high levels of r-IL-2 are required to induce minimal proliferative responses in phorbol diester induced cells irrespective of the age of the mice. Estimation of the frequency of Go T cells able to respond to Con A by expressing functional high affinity IL-2 receptor showed a significant decrease in the population of cells derived from old mice.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00095-15-LCP

PERIOD COVERED

October 1, 1987 - September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

The Role of Cell Membrane Structures on Cellular Recognition

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	W. H. Adler	Medical Officer, PHS	LCP, NIA
Others:	+J. E. Nagel	Medical Officer, PHS	LCP, NIA
	R. K. Chopra	Visiting Fellow	LCP, NIA
	W. O. Boto	NRC Fellow	LCP, NIA
	S. D. Kittur	Medical Staff Fellow	LCP, NIA
	J. J. K. Hoh	Medical Staff Fellow	LCP, NIA
	D. C. Powers	Medical Staff Fellow	LCP, NIA

COOPERATING UNITS (if any)

Drs. R. Winchurch, D. Kittur and S. Xu - Dept. of Surgery, FSK Medical Center, Johns Hopkins University, Baltimore, MD.

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Clinical Immunology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

4.2

PROFESSIONAL:

3.0

OTHER:

1.2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The effects of illness and nutritional status on various areas of the immune system are important considerations. This is especially true in attempting to define the effects of aging on immune function. Vitamin E apparently has little effect on immune function in vivo or in vitro. Burn trauma results in an overall depletion of circulating T cells, especially CD8⁺ cells. The receptor for IL-2, an activation marker, is induced not only by antigen and mitogen activation but by endotoxin. This can be seen frequently in older individuals. The T cell antigen receptor is under the control of at least 4 genes, which all are equally transcribed by an activation signal. Studies on genes involved in neurologic disorders have demonstrated that abnormal superoxide dismutase and tubulin gene transcription are not a features of Alzheimer's disease. Also, there are no common viral infections associated with this disorder.

Others:	+F. J. Chrest	Biologist	LCP, NIA
	R. S. Pyle	Bio. Lab Tech.	LCP, NIA
	B. A. Dorsey	Bio. Lab Tech.	LCP, NIA
	G. D. Collins	Biologist	LCP, NIA

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00096-15-LCP

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Lymphocyte Activation and Function in Aging Individuals

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	M. A. Brock	Research Biologist	LCP, NIA
Others:	W. H. Adler	Medical Officer, PHS	LCP, NIA
	R. S. Pyle	Bio. Lab. Tech.	LCP, NIA
	F. J. Chrest	Biologist	LCP, NIA

COOPERATING UNITS (if any)

H. J. Hoffman, D. W. Denman III, Biometry Branch, NICHD

LAB/BRANCH

Gerontology Research Center, Laboratory Clinical Physiology

SECTION

Clinical Immunology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1.2

PROFESSIONAL:

1.0

OTHER:

0.2

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The effects of agents which can perturb the cytoskeleton were studied in T lymphocytes from aging mice. Cytochalasins B and E (CB, CE) interact with the T-cell mitogen, Concanavalin A (Con A), and IL2 in activation and signal transduction of splenocytes and purified resting T cells from young (4 mo.) and senescent (24 mo.) C57BL/6 mice. After stimulating single cell suspensions with Con A, CB, CE, IL2 or various combinations of these, levels of activation were assessed by tritiated thymidine incorporation and flow cytometry.

No age-related differences were observed with stimulation of splenocytes and resting T cells by very low concentrations of cytochalasins which interact with high affinity binding sites, plasma membrane proteins. The highest levels of proliferation induced by Con A were unaffected by adding optimum concentrations of CB or CE, however both cytochalasins synergized with Con A at nonoptimum concentrations resulting in 2-3 fold increases in proliferation of splenocytes and resting T cells from both young and old mice. The levels reached 40-60% of the maximum induced by Con A alone. Higher concentrations of cytochalasins cause inhibition of glucose transport by CB but not by CE. In combination with mitogenic concentrations of Con A and IL2, CB inhibited mitogenesis in all resting T cells. CE, however, had differential effects on thymidine incorporation by resting T cells from young and old mice, inhibiting the young and enhancing the old. At these higher concentrations, CE binds to low affinity binding sites, actin, in the cytosol and depolymerizes actin. These results suggest that the state of polymerization of actin in microfilaments changes with age and contributes to the decline in T lymphocyte function.

IRP-LCP-87

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00104-12-LCP

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Clinical Immune Survey of the Longitudinal Project Participants*

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	W. H. Adler	Medical Officer	LCP, NIA
Others:	+J. E. Nagel	Medical Officer	LCP, NIA
	R. K. Chopra	Visiting Fellow	LCP, NIA
	F. J. Chrest	Biologist	LCP, NIA
	R. S. Pyle	Bio. Lab Tech.	LCP, NIA
	D. C. Powers	Medical Staff Fellow	LCP, NIA
	G. D. Collins	Biologist	LCP, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Clinical Immunology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

4.4

PROFESSIONAL:

2.8

OTHER:

1.6

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☒ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

These studies utilize participants in the Baltimore Longitudinal Study of Aging to gain insight into the genetic, biochemical and molecular mechanisms underlying age-associated changes in immune function. The projects are directed toward distinguishing and characterizing the origins of defective T cell activation and proliferation.

Others: +B. A. Dorsey
N. E. Kendig

Bio. Lab Tech.
Guest Worker

LCP, NIA
JHU, EOD 8/88

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00261-01-LCP

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Host Factors Relating to HIV Infections

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	W. H. Adler	Medical Officer, PHS	LCP, NIA
Others:	J. E. Nagel	Medical Officer, PHS	LCP, NIA
	S. D. Kittur	Medical Staff Fellow	LCP, NIA
	M. M. Bagdon	Biologist	LCP, NIA
	F. J. Chrest	Biologist	LCP, NIA
	G. D. Collins	Biologist	LCP, NIA
	R. S. Pyle	Bio. Lab Tech.	LCP, NIA
	B. A. Dorsey	Bio. Lab Tech.	LCP, NIA

COOPERATING UNITS (if any)

Dr. Clements, Vaccine Center, Johns Hopkins University, Dr. John Bartlet, Dept. Medicine, Johns Hopkins Univ., Drs. E. Dax and R. Lange, NIDA, Dr. John Johnson, Dept. Pediatrics, Univ. Maryland School Medicine, Baltimore, MD.

LAB/BRANCH

Gerontology Research Center, Laboratory Clinical Physiology

SECTION

Clinical Immunology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:
3.0

PROFESSIONAL:

1.2

OTHER:

1.8

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Ninety individuals have been screened for the HIV vaccine trial. Evaluations of immune function on individuals admitted to the trial are proceeding. The investigation of the effects of drugs on immune function has been expanded to study the effects of multiple exposure to a amyl nitrite as is seen in society, and to study the effects of THC. The Interleukin-2 receptor in serum from individuals undergoing AZT therapy provides a measure of the extent of the inflammatory process. The detection of viral genome in tissues and cells is able to be accomplished even if the concentration of virus is very low. The PCR technique is useful for detecting a nucleic acid sequence even if low levels of DNA are present.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00011-15 LCP

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Hormones and Aging. I. Adenylate Cyclase and Hormone Action

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

R.I. Gregerman, M.D., Chief, Endocrinology Section, Laboratory of Clinical
Physiology, National Institute on Aging (Retired 7/1/88)

Other: Z-H. Li Visiting Associate, LCP, NIA
H. Flamer Guest Worker, LCP, NIA
R. Carraro Visiting Fellow, LCP, NIA
M. Bellantoni Medical Staff Fellow, LCP, NIA
E. Yechiel Visiting Associate, LCP, NIA

COOPERATING UNITS (if any)

Department of Medicine, Francis Scott Key Medical Center
Endocrinology Division, University of Texas Health Sciences
Center, San Antonio

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Endocrinology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project initiates studies of age-related alterations of hormone action. Recent focus has been on the actions of hormones which act through components of cell membranes, especially those of the hormone-sensitive adenylate cyclase complex. These components include hormone receptors and regulatory proteins. Aging in fat cells is being studied in tissue culture of preadipocytes and dedifferentiated mature fat cells (postadipocytes) from rats.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00013-13 LCP

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Hormones and Aging. III. Aging and Human Endocrine Regulation

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

S. M. Harman, M.D., Senior Investigator, LCP, NIA

Other: Marc R. Blackman, M.D. Guest Scientist LCP, NIA

Michelle Bellantoni, M.D., Medical Staff Fellow LCP, NIA

Carlo Contoreggi, M.D. Medical Staff Fellow LCP, NIA

COOPERATING UNITS (if any)

Depts. of Medicine, Francis Scott Key Med. Center and J.H.U.

Medical School

Metabolism Section, LCP and LCS, GRC

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Endocrinology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS

3.0

PROFESSIONAL

2.5

OTHER

.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Continuation of this project in FY-88 has included completion of a prospective study assessing possible interactions among age, steroid hormones, and risk of coronary artery disease (CAD) in BLSA men sampled when all were free of CAD. When men who subsequently developed CAD (CARD) were compared with a group who had no CAD after a mean follow-up of 9.5 y (CRL), the CARD group had significantly higher levels of total cholesterol and blood pressure (BP). Furthermore, systolic BP and cholesterol levels segregated as risk factors by age, with cholesterol significant only for men less than 65 years old and systolic BP only for men greater than 65 years old. The CARD and CRL group mean plasma concentrations of total and free E2, T, and the ratio of E2/T did not differ significantly, suggesting that plasma levels of E2 and T in men are not independent risk factors for development of CAD. However, an increase in total plasma E2 with age, confined to the CARD group, showed a distribution pattern suggesting there to be a greater risk of CAD in young men with low plasma E2 levels. Analysis of plasma DHEA data showed a decrease with age, but no independent association of DHEA levels with CAD risk. We have also initiated an investigation of the effects of varying doses of transdermally administered E2 on menopausal symptoms, calciotropic hormone levels and calcium excretion, as well as on basal and GHRH-modulated GH secretion in healthy post-menopausal women of different ages. Another new study begun this year is an exploration of the interrelationships among sex steroid hormone metabolism, body fat distribution, and various parameters of glucose and lipid homeostasis in healthy women of different ages.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00023-12 LCP

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders)

Hormones and Aging. II. Pituitary and Hypothalamic Function in Experimental Animals

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

S. M. Harman, M.D., Ph.D., Senior Investigator, LCP, NIA

Other: M. R. Blackman, M.D. Guest Scientist LCP, NIA

George S. Roth, Ph.D. Section Chief MPGS, LCMB, NIA

K. Kochman, Ph.D. Visiting Scientist MPGS, LCMB, NIA

T. Maki, Ph.D. Visiting Scientist MPGS, LCMB, NIA

Donald K. Ingram, Ph.D. Senior Investigator, MPGS, LCMB, NIA

David Danner, M.D., Ph.D. Section Chief LMG, NIA

Carlo S. Contoreggi, M.D. Staff Fellow, ARC, NIDA

COOPERATING UNITS (if any) Molecular Physiology and Genetics Section, LCMB, GRC

Laboratory of Molecular Genetics, GRC

Laboratory of Neuroendocrinology, ARC, NIDA

Dept. of Medicine, F.S.K. Med. Center and J.H.U. Medical School

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Endocrinology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS.

2.0

PROFESSIONAL:

1.5

OTHER:

.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The secretory physiology of isolated cells and tissues from anterior pituitary glands of old vs. mature male and female rats has been studied in both static monolayer and dynamic perfusion in vitro culture systems. In monolayer culture, exposure of pituicytes from old rats to the ionophore A23187 or to the phorbol ester PMA, but not to inositol triphosphate, substantially diminished the age-related deficit in GnRH-stimulated LH secretion. Exposure to both A23187 and PMA led to a synergistic effect in cells from both mature and old rats. In addition, there was an age-related decrease in dopamine inhibition of in vitro PRL release from cells of both male and female rats. However, there was no change with age in pituitary membrane dopamine receptor binding in either sex, suggesting that post-receptor alterations were responsible for the decreased dopamine action with age on the lactotrope. In perfusion culture, coupled hypothalami and anterior pituitary tissues from young adult rats exhibited rhythmic PRL and ACTH secretion, apparently modulated by factors (e.g. dopamine and CRH) from the hypothalamic fragments, providing a model for future aging studies. Molecular genetic experiments revealed no increase with age in stable PRL mRNA, but a decrease in LH-beta mRNA, in pituitary tissues and cells from intact and ovariectomized female rats. The interactive effects of diet and age on testis and thyroid function were evaluated in male Rhesus and Squirrel monkeys.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00204-5 LCP

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (60 characters or less. Title must fit on one line between the borders.)

Metabolic Studies in the Baltimore Longitudinal Study of Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Reubin Andres

Chief, Metabolism Section, LCP, NIA

Other Investigators:

Jordan Tobin

Chief, Applied Physiology Section, LCP, NIA

Judith Hallfrisch

Senior Staff Fellow, LCP, NIA

Hiroshi Shimokata

Visiting Fellow, LCP, NIA

Donald Drinkwater

Visiting Fellow, LCP, NIA

Denis Muller

Chemist, Metabolism Section, LCP, NIA

Janet Sobell, Gladys Block

Div. Cancer Prev. & Control, NCI

COOPERATING UNITS (if any)

Div. of Geriatric Medicine & Gerontology, Dept. of Medicine, FSKMC, JHU

Janette Busby and Patricia Coon

Epistat, Inc. Patricia Koslome

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

3.4

PROFESSIONAL

1.8

OTHER

1.6

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Aging is characterized by a host of changes in metabolic variables which have profound effects on disease development and on survival. The BLSA provides the opportunity to conduct analyses on these variables to relate them to other characteristics of the individual, and to analyze for long-term effects of these complex interactions. Variables which are potentially alterable by changes in life style characteristics (diet, body weight, activity level) are of especial importance in this respect. Age-specific normative data are required and can only be determined rationally by analyses such as these. Dietary diary information has been obtained on 600 men and women. This has provided an important update on secular changes in the diet since the 1961-1976 dietary analyses were published. The dietary trends seen from the 1960s to the 1970s have continued into the 1980s. Total caloric intake decreased, calories from fat were partially replaced by calories from carbohydrate, the polyunsaturated; saturated fatty acid ratio increased further and cholesterol intake continued to fall. Crude fiber intake rose. These favorable trends were seen in all age groups from young to middle-aged and old adults. Collaborative studies with NCI scientists showed that remote dietary habits (10-14 years in the past) could be obtained by personal interview with remarkable validity. BLSA men who had provided 7-day dietary diaries in 1971-1975 were contacted in 1985. The use of a self-administered dietary questionnaire will provide less satisfactory data unless personal instruction and follow-up call-backs are included in the process. Interestingly, age itself did not influence the accuracy of the results. These results indicate that long-term dietary histories - an important methodologic requirement for testing theories of the dietary causation of a number of important illnesses - can be obtained with remarkable accuracy.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00205-5 LCP

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Body Fat Distribution Pattern in the Baltimore Longitudinal Study of Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

Reubin Andres

Chief, Metabolism Section, LCP, NIA

Other Investigators:

Denis Muller

Chemist, Metabolism Section, LCP, NIA

Hiroshi Shimokata

Visiting Fellow, Metabolism Section, LCP, NIA

Jerome Fleg

Scientist, LCS, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

2.1

PROFESSIONAL:

1.5

OTHER:

0.6

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A remarkable variety of clinical variables have been shown to be related to the body fat distribution. Many studies have shown that the waist hip ratio (WHR) is not only a simple index of the fat distribution pattern, but is also a powerful predictor of risk factors, diseases, and mortality. Despite extensive literature, systematic information on the distribution of values for the two components of the WHR (waist and hip circumference), for the ratio itself, and for changes in these values with change of weight is not available. The effects of age, sex and change in weight on WHR have been examined in the BLSA subjects. The effects of age, WHR, body fatness, and physical activity and fitness levels have been examined with respect to their contribution to the variance in glucose tolerance. In step-wise multiple regression analyses, age remains as an independent significant correlate. Fatness and WHR also enter as significant determinants. Physical activity level and physical fitness make very little contribution in either men or women, but may still exert an important effect by influencing body fatness. An analysis of the effects of cigarette smoking on the pattern of distribution of body fat has produced surprising results. In BLSA men, cigarette smokers (S) were leaner than non-smokers (non-S) except for the heaviest smokers. Despite the generally lower body weights in smokers, the WHR rose progressively with the number of cigarettes smoked. Furthermore, a change in smoking habit (S to non-S or non-S to S) gave unexpected results when the changes in body weight were considered. Despite the gain in weight in the "quitters" (S to non-S group), WHR did not increase; in the "starters" (non-S to S), despite weight loss, the WHR actually increased. Thus, the decision to initiate or to continue smoking in order to control body weight is doubly unwise from the health standpoint. The direct harmful effects of smoking will be reinforced by a more dangerous pattern of fat distribution. Furthermore, smokers who quit can be reassured that their weight gain (not an obligatory result of course) will at least not cause any worsening of their fat distribution pattern.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00208-4 LCP

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Aging, Obesity, Physical Activity and Endocrine-Metabolic Function

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Reubin Andres

Chief, Metabolism Section, LCP, NIA

Other Investigators:

Donald Drinkwater

Visiting Fellow, LCP, NIA

Roy Verdery

Medical Staff Fellow, LCP, NIA

Howard Baldwin

Chemist, Metabolism Section, LCP, NIA

Mary E. Bannon

Biologist, Metabolism Section, LCP, NIA

Denis Muller

Chemist, Metabolism Section, LCP, NIA

Faye Barrack

Lab Tech, Metabolism Section, LCP, NIA

COOPERATING UNITS (if any)

Francis Scott Key Medical Center, the Johns Hopkins University

Andrew Goldberg

Eugene Bleecker

Loretta Lakatta

Patricia Coon

Ellen Rogus

Adriane Kozlovsky

Marilyn Lumpkin

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

2.3

PROFESSIONAL:

0.7

OTHER:

1.6

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Obesity, sedentariness and aging are associated with declines in lipid, glucose and adipose tissue metabolism, and altered sympathoadrenal responsiveness. To determine the interrelationships among these variables, this study examines metabolic and sympathoadrenal functions in healthy, obese, sedentary men aged 45-75 years at entry into the study and after weight reduction or aerobic exercise training. The metabolic functions evaluated are: 1) glucose tolerance; 2) insulin secretion and sensitivity assessed by euglycemic and hyperglycemic clamps; 3) lipoprotein lipid profiles, high density lipoprotein (HDL) subspecies levels, and postheparin plasma lipoprotein lipase and hepatic lipase activity; 4) the regulation of adipose tissue lipolysis and fat cell size by physical fitness (VO₂max), fatness (% body fat), and the regional distribution of body fat (waist:hip circumferential ratio) by measuring the responsiveness of biopsied adipose tissue from upper and lower body sites to beta- and alpha2-adrenergic stimuli and by the activity of lipoprotein lipase; and 5) sympathoadrenal responses to upright posture. A total of 152 subjects have completed baseline metabolic studies and have been randomized to either the weight reduction or aerobic exercise training interventions. Thirty-eight subjects have completed the weight loss program and 27 the exercise program. With weight loss of >5% body weight with no change in VO₂max, there was a significant improvement in most of the metabolic variables. In 27 subjects whose VO₂max increased >10%, triglyceride decreased but other metabolic variables did not change. Subjects completing both interventions demonstrated complementary effects on metabolic function. In addition to the subjects who have completed their interventions, there are currently 31 subjects in progress in the weight loss group and 33 in the exercise group. These metabolic studies are a collaborative effort of scientists in the Metabolism Section, LCP, NIA and in the Division of Geriatric Medicine and Gerontology, Department of Medicine, the Johns Hopkins University.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00209-4 LCP

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Physical Fitness and Metabolic Functions: Studies on Senior Athletes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Reubin Andres

Chief, Metabolism Section, LCP, NIA

Other Investigators:

Roy Verdery

Medical Staff Fellow, LCP, NIA

Donald Drinkwater

Visiting Fellow, LCP, NIA

Howard Baldwin

Chemist, Metabolism Section, LCP, NIA

Mary E. Bannon

Biologist, Metabolism Section, LCP, NIA

Denis Muller

Chemist, Metabolism Section, LCP, NIA

Faye Barrack

Lab Tech, Metabolism Section, LCP, NIA

COOPERATING UNITS (if any)

Francis Scott Key Medical Center, the Johns Hopkins University

Andrew Goldberg

Eugene Bleecker

Loretta Lakatta

Patricia Coon

Ellen Rogus

Adriane Kozlovsky

Debbie Meyers

Janette Busby

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

2.3

PROFESSIONAL:

0.7

OTHER:

1.6

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Older people are prone to develop glucose intolerance, hyperinsulinemia, hyperlipidemia, and obesity, all of which are metabolic risk factors for atherosclerosis. These declines in metabolic function with aging may not be due to biological aging process per se, but may be related more to lifestyle changes of increasing sedentariness and overeating with resultant deconditioning and obesity. The effects of physical conditioning on metabolic function in older men are examined in this project by controlling for factors, such as disease, age, cigarette smoking and alcohol, which affect function and by measuring other confounding variables such as body composition (% body fat and its distribution), diet, and aerobic capacity (V02max). The mechanisms by which physical conditioning and body composition affect glucose, lipid and adipose tissue metabolism are studied in selected disease-free lean and obese older men with a spectrum of V02max (20-60 ml/kg.min). Sixty-four men, 55-75 years of age have been carefully screened for disease. A subset have undergone measurements of: (a) glucose tolerance, insulin sensitivity and secretion (glucose clamp); (b) insulin binding and autophosphorylation; (c) fasting and postprandial lipoprotein lipids and HDL subspecies; (d) postheparin plasma lipoprotein lipase (LDL) and hepatic lipase activities, and (e) adipose tissue LPL activity and the regulation of lipolysis by adrenergic agonists. Results suggest that obesity and V02max interact to regulate metabolic function in older men. Longitudinal interventions are in progress to determine mechanisms by which differences in V02max and body composition affect glucose, lipid, and adipose tissue metabolism. Reevaluation in a few subjects suggests that convergence of lean men to similar V02max and obese men to V02max and % body fat equivalent to the leaner men, narrows differences in metabolic function. This suggests that lifestyle habits, not aging per se, are major determinants of certain metabolic functions in older men.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00021-25 LCP

PERIOD COVERED October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Study of Normal Human Variability and Cross Cultural Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

Principal Investigators:

C.C. Plato	Sr. Research Geneticist	LCP NIA
J.D. Tobin	Chief, Applied Physiology Section	LCP NIA
Others:		
E. Schneider	Acting Chief	LMG NIA
J. White	Biologist	LMG NIA

COOPERATING UNITS (if any)

Gajdusek, CNS NINCDS; Garruto, CNS NINCDS; Yanagihara, CNS NINCDS;
Carter, CPSB NCI; Fox, University MD; Rudan, University Zagreb, Yugoslavia

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Applied Physiology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

0.65

PROFESSIONAL:

0.25

OTHER

0.40

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project represents an ongoing collaborative effort, involving WHO and other national and international laboratories to coordinate the collection, evaluation and interpretation of normal genetic markers in order to study the cross-cultural patterns of genetic and extraneous factors as they relate to normative aging and to diseases with late onset. Specifically, the objectives of this study are: A) To study the distribution of DNA minisatellites, dermatoglyphics, lateral dominance and other genetic variables in BLSA participants and other control samples, as well as in patients with late onset diseases. B) To study the genetic segregation of these markers in families with late onset diseases, such as Alzheimer's disease, breast cancer, ALS and others, in an effort to establish genetic linkages and eventual identification of the factors responsible for these diseases and C) To study the cross cultural patterns of genetic and non genetic factors in an effort to better understand the process of normative aging.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00022-12 LCP

PERIOD COVERED October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Investigations of Bone Mineral Density and Bone Loss

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Principal Investigators:

C.C. Plato	Sr. Research Geneticist	LCP NIA
J.D. Tobin	Chief, Applied Physiology	LCP NIA
Others:		
S. Sherman	Fellow	LCP NIA

COOPERATING UNITS (if any)

University Zagreb, Yugoslavia; Nihon University, Tokyo, Japan; Univ. Maryland; Francis Scott Key Medical Ctr.; Johns Hopkins Univ.; CNS, NINCDS.

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Applied Physiology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS

4.40

PROFESSIONAL

1.95

OTHER

2.45

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Bone loss together with osteoarthritis (see project Z01 AG 00290-03 LCP entitled "Osteoarthritis and Aging") is one of the two principal age related changes of the human skeleton. Even though these changes are considered universal phenomena inherent to aging, they may result in incapacitating ailments. Advanced bone loss may result in osteoporosis and frequent bone fractures. At some time during the fourth decade of life, the human skeleton begins to lose bone. That is, bone mass decreases in relation to bone volume. In tabular bones, cortical bone is resorbed from the endosteal surface. Because of the thinning of the cortical bone shell, bones lose their mechanical integrity and fracture more readily. The trabecular bone mass of the vertebral column also decreases with age. The vertebral plates decrease in density, lose resistance to vertical compression stress and are more vulnerable to vertebral collapse. Vertebral compression fractures and fractures of the femoral neck are the most serious consequences of bone loss. The following skeletal sites are involved in the present study: hand-wrist, ulna and radius, vertebral column and the proximal femur (trochanter, neck and Ward's triangle). This project deals with the epidemiological, genetic, cross-sectional, longitudinal and biochemical aspects of bone loss (1) among the participants of the Baltimore Longitudinal Study, (2) in a sample of normal adult Guamanians (Chamorros), (3) in genetic isolates in Croatian Islands of Yugoslavia, (4) among patients afflicted with Amyotrophic Lateral Sclerosis/Parkinsonism Dementia Complex of Guam, (5) in long distance runners and relatively inactive normal controls, and (6) in rats and other animals.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00028-12 LCP

PERIOD COVERED October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders)

Epidemiological & Genetic Studies of ALS/PD Complex of Guam

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

Principal Investigators:

C.C. Plato	Sr. Research Geneticist	LCP NIA
J.D. Tobin	Chief, Applied Physiology Section	LCP NIA

COOPERATING UNITS (if any)
D.C. Gajdusek, Chief, CNS NINCDS
R.M. Garruto, Sr. Staff Associate, CNS NINCDS
R.T. Yanagihara, Research Associate, CNS NINCDS
K.M. Fox, Epidemiologist, University of MD

LAB/BRANCH Gerontology Research Center, Laboratory of Clinical Physiology

SECTION Applied Physiology Section

INSTITUTE AND LOCATION NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS	0.25	PROFESSIONAL	0.15	OTHER	0.10
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CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided)

This project represents further efforts to elucidate the etiology of high incidence of Amyotrophic Lateral Sclerosis (ALS) and Parkinsonism Dementia (PD) on the island of Guam. A patient-control prospective study (Registry) was established in 1958. The objective of the registry has been to determine (1) whether relatives of ALS and PD patients have higher risk for developing the disease than relatives of controls and (2) if familial occurrence does exist, to determine the extent of genetic involvement in the etiology of the disease. A twenty-five year follow-up analysis of the registry has been concluded and the results were published. The registries are now being maintained for future follow-up studies.

Other objectives of this study are: 1) to investigate the genetic and epidemiological factors contributing to the very high incidence of Amyotrophic Lateral Sclerosis and Parkinsonism Dementia (ALS/PD) on Guam; 2) to evaluate the distribution of the various established genetic and anthropological markers among the normal Guamanian population and compare them with those of the ALS/PD patients; and 3) to ascertain the effects of immobilization due to paralysis on bone density.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00290-03 LCP

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Osteoarthritis and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

Principal Investigators:

D.A. Kallman IRTA Fellow LCP NIA

J.D. Tobin Chief, Applied Physiology Section LCP NIA

Others:

C.C. Plato Senior Research Geneticist LCP NIA

COOPERATING UNITS (if any)

Frances Scott Key Medical Center (Wigley); Johns Hopkins Hospital (Scott and Hochbert); Laboratory of Personality & Cognition, NIA (Costa)

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Applied Physiology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS

1.35

PROFESSIONAL

1.05

OTHER

0.30

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither☐ (a1) Minors☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The most common rheumatic disease of the elderly is osteoarthritis (OA). Forty million Americans are estimated to have radiological evidence of OA; the majority are asymptomatic. However, a controversy exists regarding the ability of the established radiographic OA grading scale to describe the natural history of the disease accurately. The Kellgren method of grading radiographic evidence of OA has been accepted as the "gold standard" since its description in 1957. The Kellgren scale has some shortcomings, however. Most notably, the OA status of many joints doesn't fit easily into the Kellgren grading system. By reading hand/wrist x-rays for individual features as well as by an overall Kellgren grade, it may be possible to devise a new more useful grading methodology.

Radiographic measures of OA may be insensitive to early stages when the only findings are cartilage erosions. Magnetic resonance imaging (MRI) of joints may provide a better method of visualizing early osteoarthritis.

There are two current projects to evaluate osteoarthritis: joint radiography and MRI. The joint radiography project is both a methodology study to examine the reproducibility of scores of joint abnormalities as rated by several observers, and a longitudinal study designed to determine the progression of osteoarthritis by evaluation of these changes. The interrelationship of symptoms, physical exams, and x-rays in several joints will also be examined.

The magnetic resonance imaging project is designed to establish whether MRI can visualize joint abnormalities in subjects with knee pain and normal radiographs, and thus to further elucidate the natural history of OA and other joint abnormalities.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00291-03 LCP

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Physiology of Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

Principal Investigators:

Jordan D. Tobin Chief, Applied Physiology Section LCP NIA

Others:

Douglas Kaliman Applied Physiology Section LCP NIA

Chris Plato Applied physiology Section LCP NIA

Judy Halfrisch Metabolism Section LCP NIA

David Arenberg Cognition Section LPC NIA

Jerome Fleg Cardiac Function Section LCS NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Applied Physiology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

0.70

PROFESSIONAL

0.55

OTHER:

0.15

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Studies of age changes in physiologic systems have included renal, cardiovascular, and metabolic areas. Renal glomerular filtration rate as estimated by 24 hr creatinine clearance was not related to cardiac performance as estimated by resting or exercise cardiac output. Thus the age differences in renal function cannot be considered either as a marker for age changes in other systems nor as a result of primary changes in the cardiovascular system.

Glucose metabolism as assessed by performance on a glucose tolerance test was not related to cognitive performance as assessed either by tests of memory or problem solving when age, education, obesity or disease were taken into account.

Cross-sectional and longitudinal analyses agree that grip strength declines at an accelerating rate after age 40. However, the grip strength of a sizable proportion of individuals does not decrease, and this is true even in aged subjects. With advancing age, grip strength deteriorates more than is predicted by the age-related decline in muscle mass.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00292-02 LCP

PERIOD COVERED

August 1, 1987 to July 31, 1988

TITLE OF PROJECT (80 characters or less Title must fit on one line between the borders)

BLSA Physical Activity Questionnaire Study

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

Principal Investigators:

Linda P. Fried	Visiting Scientist	LCP NIA
Jordan D. Tobin	Chief, Applied Physiology Section	LCP NIA
Others:		
J. Fleg	Cardiac Function Section	LCS NIA
J. Fozard	Chief, Longitudinal Studies Branch	NIA
E. Lakatta	Chief, Laboratory of	NIA
	Cardiovascular Science	

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Applied Physiology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS

.95

PROFESSIONAL

.45

OTHER

0.5

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type Do not exceed the space provided)

This project is designed to determine the reliability and validity of questionnaire components in relation to physiologic measures of physical activity and fitness. This study consists of (1) a retrospective analysis of physical activity data collected biannually in the BLSA to describe change in physical activity levels over time and variation by age and sex, and the questions most strongly associated with treadmill-assessed fitness; (2) a prospectively-administered questionnaire to assess reliability of retrospective recall of physical activity as compared with previous self-report; and (3) prospective discrimination of the relationships between treadmill-measured fitness and daily activity (as measured by activity monitor and activity diary) with questionnaire assessment of habitual physical activity. This study will result in development of a questionnaire to assess physical activity levels in the BLSA population that has optimal validity for adults of all ages, and for both men and women. Development of such an instrument will maximize the validity of studies on the relationship between habitual physical activity levels and aging, health, and disease.

ANNUAL REPORT OF THE LABORATORY OF MOLECULAR GENETICS

Analysis of changes in hormone expression with age

M. Harman and M. Blackman, LCP, NIA, have shown that basal and stimulated levels of luteinizing hormone decline with age in the rat pituitary, and G. Roth, LCMB, NIA, has shown that basal and stimulated levels of prolactin increase in the same system. We have been investigating the mechanisms that produce these age-related hormone changes by analyzing the level of messenger RNA produced by the hormone genes as a function of age. Messenger RNAs from intact pituitary cells and from pituitary cells passaged briefly in tissue culture have been quantitated using hybridization with radioactive cDNAs, and these levels have been compared to the corresponding hormone levels measured by radioimmunoassay. Interestingly, prolactin message does not change with age while luteinizing hormone message does. This indicates that the age-related changes in these hormones are implemented by two different molecular mechanisms, one transcriptional and one translational.

Molecular genetic analysis of Alzheimer's disease

J. Blass at Cornell has shown that the activity of three thiamine-dependent enzymes--transketolase, alphaketoglutarate dehydrogenase, and pyruvate dehydrogenase--are decreased in two dementias, Wernicke-Korsakoff Syndrome and Alzheimer's disease. In general, this decrease occurs in body tissues not directly affected by the disease process; this suggests that inactivation of these enzymes is not simply an effect of the underlying pathology but may be intimately related to the cause of each disease, perhaps directly or perhaps as a predisposing factor. The goal of this project is to pursue this idea at the molecular level by cloning the gene for transketolase. A lambda gt11 library of possible clones has been screened using an anti-transketolase antibody, but unfortunately this antibody was only able to pick out clones corresponding to transferrin. This collaborative project is therefore on hold until the Blass laboratory can produce a more specific antibody.

Cloning of a gene involved in shutting off cell growth

J. Smith at Baylor has shown that when poly(A)+ RNA derived from human diploid fibroblasts at late passage is microinjected into the same cell type at early passage, the growth of the early passage cells is halted. A functionally identical activity derived from rat liver (by K. McClung and J. Smith) has a single molecular weight peak of activity on sucrose gradients. These data suggest that a single messenger RNA has the ability to shut off cell growth, and dilution experiments suggest that the message is abundant (1/100-1/1000 of total message). We are attempting to clone this mRNA by two different methods: 1) hybrid selection screening of a cDNA library, and 2) construction of a cDNA library in a T7 vector that should permit us to make

synthetic mRNAs that can be tested directly by microinjection.

Identification of age-related transcripts in the mouse

We are searching for genes whose messenger RNAs are differentially produced during the lifespan of mice. Our approach to this analysis has been to make cDNA libraries from young (3 month) and old (27 month) mice from the GRC colony. These libraries have been pooled and analyzed by hybridization techniques to see what RNA messages are present in higher copy in young or old age. Several interesting cDNAs have been found. One clone whose mRNA is specific to young liver and falls about 10-fold with age has been shown to be alpha-2-urinary globulin by DNA sequence analysis; this gene has already been shown by others to have this pattern of expression. Another clone was shown to be creatinine kinase, and its message was found to increase 3-4 fold with age in the brain. Two other clones have mRNAs that increase 3-5 fold with age, one spleen-specific and one liver-specific.

Effect of in vivo and in vitro aging on neoplastic transformation

The relationship between aging and carcinogenesis was explored by transforming cultured cells derived from various sources with oncogenes. To mimic the in vivo state, we prepared primary culture cells from lung and skin tissues. Young and old rats were mainly used as donors. For in vitro studies fibroblasts from human fetal lung and rat whole embryos were passaged to appropriate population doublings. Cells were transfected with the calcium phosphate precipitated oncogene DNA, then subjected to a focus assay. The number of foci, which indicate the number of transformed cells, were examined to determine if older cells respond differently to the oncogenes than younger cells. Our results indicate that cellular aging alters the intrinsic susceptibility to oncogene induced neoplastic changes at the cellular level.

Aberrant gene expression and aging

R. Cutler, LCMB, NIA, has suggested that a possible mechanism of aging may be "dysdifferentiation": the loss of control of gene expression by aging cells, so that genes become aberrantly expressed in old age. This idea was based on his observation that globin message was present in liver and brain cells of mice, and that this level increased with age. Recent findings have provided additional evidence that this idea may be relevant to aging: it has been shown that methylation of DNA (associated with the shutdown of gene expression) decreases with age and that genes on Lyonized X-chromosomes frequently become active in old age. We have chosen five genes, each specific to a different tissue, and asked whether any of them is expressed in any other of the tissues in old age. No such change was found at the one copy per cell level.

Isolation of genes differentially expressed in brain of old and young rats

Despite the structural, and biochemical changes reported to occur in aging brain, the mechanism(s) underlying the aging process itself remain unknown. Thus, we have begun a new project designed to explore differential gene expression in old and young rat brain. Using subtraction hybridization techniques we are attempting to clone genes which are differentially expressed in aged (24 month) and mature young (5 month) rats. Briefly, the basic approach is to construct two cDNA libraries; one from poly A+ RNA from young rats, the other from poly A+ RNA from old rats. Poly A+ RNA from one age group is hybridized to the cDNA derived from the opposite age group and the cDNA/mRNA hybrids removed. As a result, nonhybridizing cDNAs obtained and subsequently packaged in a bacterial vector, should be enriched or highly specific for a particular age group. Ultimately, this will give us the opportunity to identify and study those genes which are involved (associated) with the aging process in brain by virtue of their increased expression (or conversely, by their relative inactivity) at specific ages. Both libraries have been constructed and are currently being screened to identify cDNAs which are expressed differentially in old and young rats.

Regulation of Interleukin 2 gene expression in lymphoid and nonlymphoid cells

This project is focused on understanding the basic control mechanisms responsible for expression of the human interleukin 2 (IL-2) gene. IL-2 gene expression is tightly controlled and limited to antigenic stimulation of T cells. In order to study the cell specific regulation of the IL-2 gene we have transfected the human IL-2 gene into mouse NIH-3T3 fibroblasts, human HeLa cells and mouse BFS lymphoma T cells and subsequently analyzed stable transformant cells containing the introduced gene for its expression. All three cell lines were found to express the foreign gene constitutively albeit at low levels. This was evidenced by the presence of both immunoprecipitable protein and bioactivity characteristic of IL-2 in cellular supernatants, as well as mRNA in cellular extracts which hybridized to a human IL-2 cDNA. Curiously, the mRNA species seen was larger than expected for human IL-2 and appears to contain intronic sequences. Treatment with phorbol myristate acetate and the calcium ionophore A23187 resulted in increased expression of the transfected human IL-2 gene in BFS cells but not in 3T3 or HeLa cells. We conclude that the human IL-2 gene transfected into lymphoid and nonlymphoid cells is constitutively expressed while its protein kinase C/calcium-mediated inducible expression remains restricted to lymphoid cells. Our data are consistent with the occurrence of an imbalance of the interplay of positive and negative regulatory DNA sequences modulating IL-2 gene expression and provide a useful experimental model for their investigation.

HSP 70 expression in cultured fibroblasts from young and aged rats

Given that defects in thermoregulation and susceptibility to hyperthermia increase in older individuals, our studies are directed at determining if the response to heat induced stress is altered in old rats when compared to young cohorts. Our approach involves the isolation and establishment of primary skin and lung fibroblast cultures grown to confluence. Subsequently, a cloned mouse cDNA probe for heat shock protein HSP 70 mRNA is used to measure HSP 70 mRNA levels in the cultures by northern blotting before and after heat shock. Preliminary experiments were performed to optimize heat shock conditions for the fibroblasts. In both old and young cultures the highest HSP 70 induction was obtained with treatment at 42.5 C for 90 min followed by a recovery period of 120 min. Using these conditions we have found that fibroblast cultures derived from both skin and lung of old rats show lower accumulation of HSP 70 mRNA than those of young rats. Preliminary experiments analyzing HSP 70 protein show a correlative decrease in HSP 70 protein in aged animals. This decline in the induction of HSP 70 mRNA and protein in fibroblasts from old rats suggests an age-related decline in the ability of these cells to respond to heat induced stress.

Molecular basis for decreased immune function in aging humans and rats

It is well established from human and animal studies that there is a general decrease in immune function that occurs with aging. This project focuses on examining the cause(s) for this decline at the molecular level. We have shown that activation by phytohemmagglutinin (PHA) of human lymphocytes from aged individuals is impaired as demonstrated by lower 3H-thymidine incorporation, and decreased synthesis and mRNA expression of interleukin 2 (IL-2) and its receptor (IL-2R). Assessment of the same parameters of T cell activation using combined treatment with the phorbol ester PMA and the calcium ionophore A23187 revealed that elderly individuals again displayed lower 3H-thymidine incorporation but showed no impairment in the expression of IL-2 or IL-2R. PHA is a mitogen which acts nonspecifically through the T cell receptor for antigen, while PMA and A23187 bypass the surface receptor. Thus our findings suggest that the defect in IL-2 and IL-2R expression seen in elderly individuals is associated with alterations in the cell surface antigen receptor complex rather than with a defect in the IL-2 and IL-2R gene loci or regulatory elements. Furthermore, these results indicate that additional factors other than decreased expression of IL-2 and IL-2R are responsible for the diminished proliferative capacity of lymphocytes seen as a function of aging.

Isolation of a new gene associated with cessation of growth

Dr. Fornace isolated a partial cDNA sequence from UV treated Chinese Hamster Ovary cells which displays a unique pattern of

Chinese Hamster Ovary cells which displays a unique pattern of expression during cell growth. This clone which was originally isolated because it was induced about 3 fold after treatment with UV is highly expressed in a variety of cell types when growth is inhibited. Using the partial cDNA sequence as a probe we have recently succeeded in isolating a full length clone corresponding to this gene product and sequenced it in its entirety. Our current studies are aimed at understanding the regulation of this gene and its relationship to cellular senescence as a model for in vitro aging.

Genetic rearrangements in prostatic hyperplasia

Several high resolution molecular genetic techniques have been successful in identifying and localizing chromosomal defects in solid tumors. However, researchers have been largely unsuccessful in finding consistent defects in prostatic adenocarcinoma (CaP) and benign prostatic hypertrophy (BPH). A relatively new application of the conventional RFLP technique, DNA fingerprinting, has shown some promise in revealing differences between tumor and normal DNA. We have used this technology to screen 14 examples of CaP and 12 examples of BPH. Seventy percent of carcinomas screened had evidence of chromosomal alterations. Unexpectedly, 33% of BPH samples exhibited detectable changes also. The genetic rearrangements may be important markers for the carcinoma, while those detected in BPH may precede those in CaP.

Studies of DNA repair and aging

The focus of this study is to examine if age-dependent alterations exist in the abilities of human cells to repair DNA damage. The emphasis of these studies will be to examine isolated cell populations that may be functionally important to aging.

Aging and UV repair of a transcribed plasmid sequence

We studied the effect of aging on the repair of a vector containing the chloramphenicol acetyl transferase gene.

This methodology more closely approximates in vivo DNA repair than other methods in that only repair of transcribed segments is measured. Techniques employing these shuttle vectors have been proved to be accurate and reproducible in several studies.

No differences in repair were found in studies of primary cultured rat embryo fibroblasts from young and old donors. In addition the repair capacity of rat embryo fibroblasts did not display any change with passage level. A study of repair in human fibroblasts from donors of various ages has been begun using the shuttle vector system.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00701-03 LMG

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (20 characters or less. Title must fit on one line between the borders.)

Studies of DNA repair and aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I.:	E.L. Schneider	Chief	LMG, NIA
Others:	N.P. Singh	Visiting Associate	LMG, NIA
	D.B. Danner	Senior Staff Fellow	LMG, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

1.2

PROFESSIONAL:

1.2

OTHER:

0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

The focus of this study is to examine if age-dependent alterations exist in the abilities of human cells to repair DNA damage. The emphasis of these studies will be to examine isolated cell populations that may be functionally important to aging.

NOTICE OF INTRAMURAL RESEARCH PROJECT

201 AG 00702-03 LMG

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effect of In Vivo and In Vitro Aging on Neoplastic Transformation

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.- E. L. Schneider, Acting Chief, LMG, NIA
Others - T. Kunisada, Former Fogarty Fellow, LMG, NIA
D. B. Danner, Senior Staff Fellow, LMG, NIA
V. Friedman, Fogarty Fellow, LMG, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

1.4

PROFESSIONAL:

1.4

OTHER:

0.0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The relationship between aging and carcinogenesis was explored by transforming cultured cells derived from various sources with oncogenes. To simulate the in vivo state, we prepared primary culture cells from lung and skin tissues. Young and old rats were mainly used as donors. For in vitro studies, fibroblasts from human fetal lung and rat whole embryos were passaged to appropriate population doublings. Cells were transfected with the calcium phosphate precipitated oncogene DNA, then subjected to a focus assay. The number of foci, which indicate the number of transformed cells, were examined to determine if older cells respond differently to the transfected oncogenes than younger cells. Our results indicate that cellular aging alters the intrinsic susceptibility to oncogene induced neoplastic changes at the cellular level.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00703-03 LMG

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Molecular Basis

for Decreased Immune Function in Aging Humans and Rats

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I. - Nikki J. Holbrook, Senior Staff Fellow, LMG, NIA

Others - Edward L. Schneider, Chief, LMG, NIA

Mike McCoy, Research Associate, LMG, NIA

COOPERATING UNITS (if any)

Laboratory of Clinical Physiology, Clinical Immunology Section,
NIA (Drs. William Adler and James Nagel)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

1.3

PROFESSIONAL:

.3

OTHER:

1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☒ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

It is well established from human and animal studies that there is a general decrease in immune function that occurs with aging. This project focuses on examining the cause(s) for this decline at the molecular level. We have shown that activation by phytohemmagglutinin (PHA) of human lymphocytes from aged individuals is impaired as demonstrated by lower 3H-thymidine incorporation, and decreased synthesis and mRNA expression of interleukin 2 (IL-2) and its receptor (IL-2R). Assessment of the same parameters of T cell activation using combined treatment with the phorbol ester PMA and the calcium ionophore A23187 revealed that elderly individuals again displayed lower 3H-thymidine incorporation but showed no impairment in the expression of IL-2 or IL-2R. PHA is a mitogen which acts nonspecifically through the T cell receptor for antigen, while PMA and A23187 bypass the surface receptor. Thus our findings suggest that the defect in IL-2 and IL-2R expression seen in elderly individuals is associated with alterations in the cell surface antigen receptor complex rather than with a defect in the IL-2 and IL-2R gene loci or regulatory elements. Furthermore, these results indicate that additional factors other than decreased expression of IL-2 and IL-2R are responsible for the diminished proliferative capacity of lymphocytes seen as a function of aging.

IRP-LMG-110

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00704-03 LMG

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Molecular Genetic Analysis of Alzheimer's Disease

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: D. B. Danner Senior Staff Fellow LMG, NIA

COOPERATING UNITS (if any)

Dementia Research Service, Division of Chronic and Degenerative Diseases, Cornell Medical College (J. Blass, R. Shue)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

0.2

PROFESSIONAL:

0.2

OTHER:

0.0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

J. Blass at Cornell has shown that the activity of three thiamine-dependent enzymes--transketolase, alphaketoglutarate dehydrogenase, and pyruvate dehydrogenase--are decreased in two dementias, Wernicke-Korsakoff Syndrome and Alzheimer's disease. In general, this decrease occurs in body tissues not directly affected by the disease process; this suggests that inactivation of these enzymes is not simply an effect of the underlying pathology but may be intimately related to the cause of each disease, perhaps directly or perhaps as a predisposing factor. The goal of this project is to pursue this idea at the molecular level by cloning the gene for transketolase. A lambda gt11 library of possible clones has been screened using an anti-transketolase antibody, but unfortunately this antibody was only able to pick out clones corresponding to transferrin. This collaborative project is therefore on hold until the Blass laboratory can produce a more specific antibody.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00705-03 LMG

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cloning of a gene involved in shutting off cell growth.

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I.: D.B. Dahner Senior Staff Fellow LMG, NIA

Others: Mark Nuell Staff Fellow LMG, NIA
E. L. Schneider Chief LMG, NIA

COOPERATING UNITS (if any)

Dept. of Virology, Baylor College of Medicine (J.R. Smith)
Noble Foundation, Ardmore, Oklahoma (K. McClung)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute of Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

1.3

PROFESSIONAL:

1.3

OTHER:

0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

J. Smith at Baylor has shown that when poly(A)+ RNA derived from human diploid fibroblasts at late passage is microinjected into the same cell type at early passage, the growth of the early passage cells is halted. A functionally identical activity derived from rat liver (by K. McClung and J. Smith) has a single molecular weight peak of activity on sucrose gradients. These data suggest that a single messenger RNA has the ability to shut off cell growth, and dilution experiments suggest that the message is abundant (1/100-1/1000 of total message). We are attempting to clone this mRNA by two different methods: 1) hybrid selection screening of a cDNA library, and 2) construction of a cDNA library in a T7 vector that should permit us to make synthetic mRNAs that can be tested directly by microinjection.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00707-03 LMG

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Regulation of
Interleukin 2 Gene Expression in Lymphoid and Nonlymphoid Cells

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I. Nikki Holbrook, Senior Staff Fellow, LMG, NIA
Others - Jennifer Luethy, Research Associate

COOPERATING UNITS (if any)

Alberto Gulino, Dipartimento di Medicina Spermentale, Universita
"LaSapienza", Roma, Italy

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

.8

PROFESSIONAL:

.25

OTHER:

.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is focused on understanding the basic control mechanisms responsible for expression of the human interleukin 2 (IL-2) gene. IL-2 gene expression is tightly controlled and limited to antigenic stimulation of T cells. In order to study the cell specific regulation of the IL-2 gene we have transfected the human IL-2 gene into mouse NIH-3T3 fibroblasts, human HeLa cells and mouse BFS lymphoma T cells and subsequently analyzed stable transformant cells containing the introduced gene for its expression. All three cell lines were found to express the foreign gene constitutively albeit at low levels. This was evidenced by the presence of both immunoprecipitable protein and bioactivity characteristic of IL-2 in cellular supernatants, as well as mRNA in cellular extracts which hybridized to a human IL-2 cDNA. Curiously, the mRNA species seen was larger than expected for human IL-2 and appears to contain intronic sequences. Treatment with phorbol myristate acetate and the calcium ionophore A23187 resulted in increased expression of the transfected human IL-2 gene in BFS cells but not in 3T3 or HeLa cells. We conclude that the human IL-2 gene transfected into lymphoid and nonlymphoid cells is constitutively expressed while its protein kinase C/calcium-mediated inducible expression remains restricted to lymphoid cells. Our data are consistent with the occurrence of an imbalance of the interplay of positive and negative regulatory DNA sequences modulating IL-2 gene expression and provide a useful experimental model for their investigation.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00708-03 LMG

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Identification of age-related transcripts in the mouse

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I.: D. B. Dannèr Senior Staff Fellow LMG, NIA

Others: V. Friedman Fogarty Fellow LMG, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

0.7

PROFESSIONAL:

0.7

OTHER:

0.0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We are searching for genes whose messenger RNAs are differentially produced during the lifespan of mice. Our approach to this analysis has been to make cDNA libraries from young (3 month) and old (27 month) mice from the GRC colony. These libraries have been pooled and analyzed by hybridization techniques to see what RNA messages are present in higher copy in young or old age. Several interesting cDNAs have been found. One clone whose mRNA is specific to young liver and falls about 10-fold with age has been shown to be alpha-2-urinary globulin by DNA sequence analysis; this gene has already been shown by others to have this pattern of expression. Another clone was shown to be creatinine kinase, and its message was found to increase 3-4 fold with age in the brain. Two other clones have mRNAs that increase 3-5 fold with age, one spleen-specific and one liver-specific.

IRP-LMG-114

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00709-03 LMG

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Analysis of changes in hormone expression with age

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I.:	D. B. Danner	Senior Staff Fellow	LMG, NIA
Others:	David Stewart	Research Associate	LMG, NIA

COOPERATING UNITS (if any)

Laboratory of Clinical Physiology, NIA (S. M. Harman, M. Blackman); Laboratory of Cellular and Molecular Biology, NIA (G. Roth).

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

1.2

PROFESSIONAL:

0.2

OTHER:

1.0

CHECK APPROPRIATE BOX(ES)

- | | | |
|---|--|--------------------------------------|
| ☐ (a) Human subjects | ☐ (b) Human tissues | ☐ (c) Neither |
| ☐ (a1) Minors | | |
| ☐ (a2) Interviews | | |

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

M. Harman and M. Blackman, LCP, NIA, have shown that basal and stimulated levels of luteinizing hormone decline with age in the rat pituitary, and G. Roth, LCMB, NIA, has shown that basal and stimulated levels of prolactin increase in the same system. We have been investigating the mechanisms that produce these age-related hormone changes by analyzing the level of messenger RNA produced by the hormone genes as a function of age. Messenger RNAs from intact pituitary cells and from pituitary cells passaged briefly in tissue culture have been quantitated using hybridization with radioactive cDNAs, and these levels have been compared to the corresponding hormone levels measured by radioimmunoassay. Interestingly, prolactin message does not change with age while luteinizing hormone message does. This indicates that the age-related changes in these hormones are implemented by two different molecular mechanisms, one transcriptional and one translational.

NOTICE OF INTRAMURAL RESEARCH PROJECT

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Isolation of
Genes Differentially Expressed in Brain of Old and Young Rats

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory and institute affiliation)

P.I. - Nikki J. Holbrook, Senior Staff Fellow, LMG, NIA
Others - Joseph Fargnoli, Senior Staff Fellow, LMG, NIA
Michael Blake, National Research Council Fellow, LMG,
NIA

COOPERATING UNITS (if any)

Laboratory of Radiation Oncology, NCI (Dr. Albert J. Fornace, Jr.)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

2.5

PROFESSIONAL:

2.0

OTHER:

.5

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Despite the structural, and biochemical changes reported to occur in aging brain, the mechanism(s) underlying the aging process itself remain unknown. Thus, we have begun a new project designed to explore differential gene expression in old and young rat brain. Using subtraction hybridization techniques we are attempting to clone genes which are differentially expressed in aged (24 month) and mature young (5 month) rats. Briefly, the basic approach is to construct two cDNA libraries; one from poly A+ RNA from young rats, the other from poly A+ RNA from old rats. Poly A+ RNA from one age group is hybridized to the cDNA derived from the opposite age group and the cDNA/mRNA hybrids removed. As a result, nonhybridizing cDNAs obtained and subsequently packaged in a bacterial vector, should be enriched or highly specific for a particular age group. Ultimately, this will give us the opportunity to identify and study those genes which are involved (associated) with the aging process in brain by virtue of their increased expression (or conversely, by their relative inactivity) at specific ages. Both libraries have been constructed and are currently being screened to identify cDNAs which are expressed differentially in old and young rats.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00712-01 LMG

PERIOD COVERED

October 1, 1987 to September 30, 1988.

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

HSP 70 Expression in Cultured Fibroblasts from Young and Aged

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I. - Nikki J. Holbrook, Senior Staff Fellow, LMG, NIA
Others - Joseph Fargnoli, Senior Staff Fellow, LMG, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

1.0

PROFESSIONAL:

1.0

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Given that defects in thermoregulation and susceptibility to hyperthermia increase in older individuals, our studies are directed at determining if the response to heat induced stress is altered in old rats when compared to young cohorts. Our approach involves the isolation and establishment of primary skin and lung fibroblast cultures grown to confluence. Subsequently, a cloned mouse cDNA probe for heat shock protein HSP 70 mRNA is used to measure HSP 70 mRNA levels in the cultures by northern blotting before and after heat shock. Preliminary experiments were performed to optimize heat shock conditions for the fibroblasts. In both old and young cultures the highest HSP 70 induction was obtained with treatment at 42.5 C for 90 min. followed by a recovery period of 120 min. Using these conditions we have found that fibroblast cultures derived from both skin and lung of old rats show lower accumulation of HSP 70 mRNA than those of young rats. Preliminary experiments analyzing HSP 70 protein show a correlative decrease in HSP 70 protein in aged animals. This decline in the induction of HSP 70 mRNA and protein in fibroblasts from old rats suggests an age-related decline in the ability of these cells to respond to heat induced stress.

IRP-LMG-117

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00713-01 LMG

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Isolation of a New Gene Associated with Cessation of Growth

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I. - Nikki J. Holbrook, Senior Staff Fellow, LMG, NIA
Others - Joseph Fargnoli, Senior Staff Fellow, LMG, NIA
Jennifer D. Luethy, Research Associate, LMG, NIA

COOPERATING UNITS (if any)

Radiation Oncology Branch, NCI (Dr. Albert J. Fornace, Jr.)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Dr. Fornace isolated a partial cDNA sequence from UV treated Chinese Hamster Ovary cells which displays a unique pattern of expression during cell growth. This clone which was originally isolated because it was induced about 3 fold after treatment with UV is highly expressed in a variety of cell types when growth is inhibited. Using the partial cDNA sequence as a probe we have recently succeeded in isolating a full length clone corresponding to this gene product and sequenced it in its entirety. Our current studies are aimed at understanding the regulation of this gene and its relationship to cellular senescence as a model for in vitro aging.

NOTICE OF INTRAMURAL RESEARCH PROJECT

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Aging and aberrant gene expression

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I.: D. B. Danner Senior Staff Fellow LMG, NIA

Others: A. I. Sato Biologist GS-7 LMG, NIA
E. L. Schneider Chief LMG, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

1.2

PROFESSIONAL:

0.2

OTHER:

1.0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

R. Cutler, LCMB, NIA, has suggested that a possible mechanism of aging may be "dysdifferentiation": the loss of control of gene expression by aging cells, so that genes become aberrantly expressed in old age. This idea was based on his observation that globin message was present in liver and brain cells of mice, and that this level increased with age. Recent findings have provided additional evidence that this idea may be relevant to aging: it has been shown that methylation of DNA (associated with the shutdown of gene expression) decreases with age and that genes on Lyonized X-chromosomes frequently become active in old age. We have chosen five genes, each specific to a different tissue, and asked whether any of them is expressed in any other of the tissues in old age. No such change was found at the one copy per cell level.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00715-01 LMG

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Aging and UV Repair of a Transcribed Plasmid Sequence

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I.: Edward L. Schneider, Chief, LMG, NIA
others: Takahiro Kunisada, Fogarty Fellow, LMG, NIA
C. Dennis Miller, NIH Postdoctoral Fellow, LMG, NIA
Michael M. Siedman, Otsuka Pharmaceutical

COOPERATING UNITS (if any)

Otsuka Pharmaceutical

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

0.5

PROFESSIONAL:

0.5

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We studied the effect of aging on the repair of a vector containing the chloramphenicol acetyl transferase gene.

This methodology more closely approximates in vivo DNA repair than other methods in that only repair of transcribed segments is measured. Techniques employing these shuttle vectors have been proved to be accurate and reproducible in several studies.

No differences in repair were found in studies of primary cultured rat embryo fibroblasts from young and old donors. In addition the repair capacity of rat embryo fibroblasts did not display any change with passage level. A study of repair in human fibroblasts from donors of various ages has begun using the shuttle vector system.

IRP-LMG-120

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00716-01 LMG

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (30 characters or less. Title must fit on one line between the borders.)

Genetic rearrangements in prostatic hyperplasia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I.:	J.J. White	Biologist	LMG, NIA
Others:	E.L. Schneider	Branch Chief	LMG, NIA
	C.D. Miller	Visiting Scientist	LMG, NIA

COOPERATING UNITS (If any)

UCLA School of Medicine, Division of Urology (Harry Neuwirth, M.D.)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

.5

PROFESSIONAL:

.5

OTHER:

CHECK APPROPRIATE BOX(ES)

- | | | |
|---|---|--------------------------------------|
| ☐ (a) Human subjects | ☒ (b) Human tissues | ☐ (c) Neither |
| ☐ (a1) Minors | | |
| ☐ (a2) Interviews | | |

SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

Several high resolution molecular genetic techniques have been successful in identifying and localizing chromosomal defects in solid tumors. However, researchers have been largely unsuccessful in finding consistent defects in prostatic adenocarcinoma (CaP) and benign prostatic hypertrophy (BPH). A relatively new application of the conventional RFLP technique, DNA fingerprinting, has shown some promise in revealing differences between tumor and normal DNA. We have used this technology to screen 14 examples of CaP and 12 examples of BPH. Seventy percent of carcinomas screened had evidence of chromosomal alterations. Unexpectedly, 33% of BPH samples exhibited detectable changes also. The genetic rearrangements may be important markers for the carcinoma, while those detected in BPH may precede those in CaP.

ANNUAL REPORT OF THE LABORATORY OF NEUROSCIENCES
NATIONAL INSTITUTE ON AGING

A. BRAIN FUNCTION IN AGING AND DEMENTIA.

1. A linear histogram method was employed to analyze brain images of glucose uptake obtained by PET in patients with DAT and in controls. Severity of dementia correlated with ratios of peak glucose uptake in frontal and parietal cortices to that in the sensorimotor cortex, indicating that regional cerebral metabolic deficits correlate with dementia severity DAT. This work was done by B. Horwitz and D. McNamara.

2. Sickle Cell Disease. Neurological dysfunction causes significant morbidity in sickle cell disease, occurring with a prevalence of 6-34%. In 6 sickle cell patients without prior neurological abnormalities, PET showed abnormal regional metabolic rates in the frontal lobe, suggesting that PET should be useful for examining cerebral dysfunction in sickle cell disease. This work was done by S. Rapoport and G. Rogers.

3. Phylogenetic hypothesis for Alzheimer's disease. PET demonstrates selective metabolic involvement of the frontal, parietal and temporal association neocortices in Alzheimer patients, but lack of involvement of primary and sensory motor regions. Furthermore, neurofibrillary tangles are selective to the association as compared to primary sensory and motor cortical regions, and Alzheimer neuropathology is found in nonneocortical brain regions which underwent rapid changes during recent hominid and higher primate evolution. These and other observations suggest that Alzheimer's disease is a phylogenetic disease which involves brain regions which underwent rapid expansion during evolution of higher primates. This work was done by S. Rapoport.

B. FUNCTIONAL INTERACTIONS BETWEEN BRAIN REGIONS.

1. Metabolic pattern in Dementia of the Alzheimer type (DAT). Regional cerebral metabolic rates (rCMRglc) obtained with PET were correlated pairwise, according to the matrix method of Horwitz et al. (1986), for mildly-to-moderately demented DAT patients and age-matched controls. The DAT group as compared with controls had fewer significant correlations between frontal and parietal lobes, of homologous correlations suggests disconnection between the right and left hemispheres in DAT, whereas the loss of ipsilateral correlations suggests hemispheric dysfunction. This work was performed by B. Horwitz.

2. Metabolic coupling in the rat brain. rCMRglc values in different regions of the rat brain were characterized by the matrix method of Horwitz et al. (1986). Large numbers of positive correlations were found between left-right homologous regions and between neocortical areas; 65% of intrahemispheric correlations were reduced in value in rats that had undergone corpus callosum contributes to integration of functional activity

between homologous hemispheric structures. Because subcortical interactions also were disrupted, the integrative role of the corpus callosum extends beyond the regions which it directly connects. This work was performed by T. Soncrant and B. Horwitz.

3. Metabolic patterns in autism. The correlation matrix approach was applied to PET data from 14 autistic men (ages 18-39 yr) and 14 controls. Compared with controls, the autistic group had significantly fewer large correlations between pairs of regions in the frontal and parietal lobes, and between subcortical nuclei and frontal/parietal regions, consistent with the view that autism represents a dysfunction in neural systems associated with directed attention. This work was directed by B. Horwitz and J. Rumsey.

4. Metabolic patterns in Down syndrome. In young Down subjects (aged 22-35 years) as compared to age-matched controls, there were fewer significant correlations among brain regions in Broca's area in the left hemisphere, consistent with language impairment, but absolute cerebral metabolic rates were not reduced. In addition, there were fewer frontal-parietal correlations, as in autistic subjects (see above), suggesting disruption of neural systems subserving directed attention. The matrix analysis shows that Down syndrome is associated with abnormal cerebral metabolic patterns related to cognitive disorders in the disease. This work was done by B. Horwitz, M. Schapiro and C. Grady.

C. NEUROLOGIC FUNCTION IN AGING AND DEMENTIA.

1. Motor activity and sleep. Patient activity monitors and self-report diaries were employed to examine wrist movements over a 9-day period in 43 healthy men aged 21 to 83 years, in their natural work and home environments. Neither the duration of the daily low activity period, nor self-reported sleep time was correlated with age. Mean daily activity, however, declined significantly with age. These results indicate reduced activity in the healthy elderly in their natural environment, but normal sleep time. This work was done by W. Renfrew.

D. BRAIN ANATOMY IN AGING AND DEMENTIA.

1. Aging in men and women. Sixty-four healthy men and 43 healthy women underwent quantitative CT. Women had smaller lateral ventricle volumes at any age, even after normalization for cranial volume. In each sex, there was a significant increase with age in the volumes of the third and left and right lateral ventricles, which was nonlinear and most pronounced in the later decades. The relation with age was the same in men and women. These results demonstrate brain atrophy with aging in men and women, and show that, in studying disease with quantitative CT, sex-matched controls must be employed. The work was conducted by J. Kaye and J. Luxenberg.

2. DAT: Longitudinal studies. Men and women with DAT and controls were studied over 6 months to 5 years with serial quantitative CT. In the male patients, mean rates of enlargement of third ventricle volume and of total lateral ventricular volumes exceeded those in controls. Female DAT patients also had significantly high rates of ventricular enlargement. There was only 5% overlap between the rates of lateral ventricular enlargement in DAT patients and controls. Rates of neuropsychological decline correlated with rates of ventricular enlargement. These results indicate that longitudinal quantitative CT studies can be used to distinguish DAT from control subjects with a high degree of certainty. This work was done by J. Luxenberg.

3. Down syndrome. Adult Down subjects with trisomy 21 karyotype were compared by quantitative CT to controls. In young Down subjects (21 to 35 yr), the volumes of gray matter and individual intracerebral structures when normalized to height did not differ significantly from control volumes. Older Down subjects demonstrated increased CSF volume indicative of brain atrophy. Thus, no observable differences exist between brains of young Down subjects and controls, after normalization for height, but aging in Down syndrome is accompanied by brain atrophy. This work was conducted by M. Schapiro.

4. Adult autism. Adult males, aged 18 to 39 years, with a childhood diagnosis of infantile autism, were compared with age-matched controls using quantitative CT. There was no statistically significant group difference on measures of cerebrospinal fluid, white matter, gray matter volumes, or subcortical nuclei volumes, indicating no gross anatomical abnormality in this syndrome. This was done in collaboration with J. Rumsey (NIMH).

5. Obsessive-compulsive disorder. Ten men with severe primary obsessive-compulsive disorder (OCD) and 10 controls were compared using quantitative CT. Caudate nucleus volume in the OCD patients was less than in the controls, but other brain morphometric measures did not differ. Reduced caudate volume supports other evidence of involvement of this structure in OCD. This work was done by J. Luxenberg.

E. CEREBROSPINAL FLUID CHEMISTRY IN AGING AND DEMENTIA.

1. CSF monoamines in DAT with extrapyramidal features (EDAT). Monoamine metabolites and biopterin in lumbar CSF were determined in DAT patients with (EDAT) and without extrapyramidal signs, and in controls. The concentrations of biopterin and of homovanillic acid were significantly less in the EDAT patients than in either the DAT patients or controls, suggesting that EDAT patients have a specific biopterin-dopaminergic central deficiency related to motor dysfunction. This work was conducted by J. Kaye and C. May.

2. CSF acetylcholinesterase and peptides in DAT and EDAT (see 1). CSF acetylcholinesterase was significantly reduced in DAT and EDAT patients as compared with controls. Somatostatin-like immunoreactivity was reduced only

in DAT patients, whereas neuropeptide Y-like immunoreactivity was unaffected in both disease. The results indicate selective deficits in DAT, cholinergic and somatostatinergic but not of neuropeptide Y. This work was conducted by J. Attack and C. May.

3. CSF markers in the myoclonic subtype of DAT. In DAT patients with myoclonus, as compared with DAT patients without myoclonus and controls, the mean concentration of homovanillic acid was reduced, as was the mean concentration of biopterin. 5-Hydroxyindole acetic acid (serotonin) concentration was higher in the myoclonic as compared to nonmyoclonic DAT group, matched for age and severity. DAT patients with myoclonus or extrapyramidal signs (see above) represent distinct subgroups with similar deficits in dopamine and biopterin, but differing with respect to serotonin metabolism. This work was done by A. Kaye, C. May and J. Attack.

F. BRAIN LIPID METABOLISM, RELATION TO FUNCTION AND AGING.

1. Mathematical model for brain incorporation of plasma palmitate. A three compartment mathematical model was developed by P. Robinson to interpret and calculate, from experimental data, the rate of palmitate uptake by brain from plasma, Jpalm. The model includes entry of palmitate from plasma into brain, de novo synthesis from acetate, and turnover of palmitate-containing brain lipids. It can be used to determine transfer constants between brain and blood, and to interpret time-dependent changes in brain radioactivity following the i.v. injection of 14C-palmitate.

2. Aging and Jpalm. H. Tabata demonstrated that Jpalm is age-invariant in adult Fischer-344 rats. As the rate of incorporation of plasma palmitate into brain represents the lower limit for turnover of brain lipids, the results are consistent with the maintenance of brain structural integrity throughout aging of the rat.

3. Brain metabolism of plasma 14C-palmitate. The distribution of radioactivity in brain metabolic pools, following the intravenous injection of (U-14C) palmitate in unanesthetized rats, was measured to examine brain metabolism of plasma-derived palmitate. At 4 hour post injection, most brain radioactivity was in lipids, mainly phospholipids, and in protein, with 25% in the aqueous aspartate and glutamate pools. Net brain radioactivity did not differ between 4 and 24 hours. The results show that, although steady-state brain radioactivity is reached within 4 hours after injection of 14C palmitate, some of this radioactivity is due to retained tracer following beta oxidation. This work was conducted by J. Miller and J. Gnaedinger.

4. Recovery mechanisms after ischemia. Unanesthetized gerbils were subjected to 5 min of bilateral carotid artery occlusion, producing an ischemic insult to the hippocampus, and Jpalm was measured for up to 7 days thereafter. Incorporation of plasma 14C-palmitate was reduced in the CA1

region of the hippocampus after 3 days, concurrent with ischemic cell death, but was elevated in the CA3, CA4 and dentate gyrus regions, concurrent with histological evidence of recovery. The palmitate method thus can be used to examine chronic reversible and irreversible brain responses to ischemic injury. The work was conducted by H. Tabata.

5. Neuronal processes recovery following axotomy. The hypoglossal nerve was unilaterally served in 3-month-old Fischer-344 rats, and Jpalm was determined bilaterally in the hypoglossal nucleus at various times thereafter. From 1 day to 24 days after axotomy, Jpalm was increased by up to 20% in the nucleus ipsilateral to the lesion, indicative of increased lipid synthesis. This study again demonstrates the utility of the palmitate method for examining brain plasticity in response to lesions. It was conducted by S. Yamazaki and J. Gnaedinger.

G. MOLECULAR BIOLOGY OF BRAIN AGING AND DISEASE.

1. Aging and brain protein synthesis. J. Cosgrove, using a cell free system, demonstrated age invariance of brain protein synthesis capacity, and no age difference in the aggregation state of polyribosome profiles obtained from brains of 3-mo-and 34-mo-old Fischer-344 rats. These results agree with reports from this laboratory that brain oxidative metabolism and palmitate incorporation generally are age invariant in the Fischer-344 rat, and point to compensatory mechanisms that maintain cerebral overall cerebral metabolism during healthy aging.

2. Nuclear proto-oncogenes in brain aging. Radiolabeled probes to detect cellular homologues of v-fos, v-myc and v-myb nuclear proto-oncogenes were hybridized with dot blocks of total brain polysomal RNA isolated from rats between 4 and 5 months old. Probes for B-actin also were used. Brain sequences corresponding to the v-fos and v-myc (but not v-myb) oncogenes were detected, but their expression did not change with age. The level of B-actin mRNA also was age-invariant. This work was conducted by M. Matocha.

3. Oncogene-related mRNA sequences and aging. Northern blot analysis showed that several s-src-related transcripts are age-invariant in the rat brain. RNA isolated from liver or brain showed that the transcript levels of c-myc, but not of c-sis or c-src-related genes, were elevated in the liver but not in the brain in relation to age, demonstrating organ specific differences in expression during aging. This work was directed by M. Matocha.

H. NEUROCHEMISTRY IN RELATION TO AGE AND DISEASE.

1. Nucleus basalis model for Alzheimer's disease. The nucleus neocortex, shows significant cell loss and pathology in the post-mortem Alzheimer brain. Based on this, a model was established by lesioning the rat nucleus basalis Meynert bilaterally. M2 muscarinic receptors fell bilaterally in the neocortex at 1 week after lesioning but recovered by 3 months, whereas the M2 receptors were normal at 1 week but were reduced bilaterally in the neocortex at 3 months after lesioning. Thus, complex and nonuniform changes

in cortical cholinergic receptors follow loss of input from the nucleus basalis. The study was performed by J. Attack.

2. Plasma proteins in normal human brain. Strong immunopositive staining was consistently seen in various regions of the normal postmortem human brain, using antibodies against albumin, acid glycoprotein and transferrin, particularly in the cerebral cortex, thalamus, hypothalamus, and dentate nucleus of cerebellum. In the pons and medulla, cranial nerves were always strongly positive. These results demonstrate plasma protein in postmortem, formalin-fixed brain, possible in relation to retrograde transport from the periphery, and suggest that similar findings in Alzheimer's disease do not reflect breakdown of the blood-brain barrier, as has been suggested. This work was done by J. Attack and H. Liu.

I. BLOOD-BRAIN BARRIER AND CENTRAL NERVOUS SYSTEM FUNCTION.

1. Osmotic opening to interferon. Interferon, which has anticancer and antiviral activities, is a protein which is prevented from entering the brain by the blood-brain barrier. Following intravenous injection of human lymphoblastoid interferon into rats, alpha-interferon was found in all tissues but brain. However, osmotic barrier opening with intracarotid 1.8 molal arabinose caused significant brain uptake. The method in humans may prove valuable for treating encephalitis from rabies or the AIDS retrovirus, or primary brain tumors with an intact blood-brain barrier. This work was conducted by N. Greig and W.R. Fredericks.

2. Protein binding of drugs affect brain uptakes. The blood-brain barrier is impermeant to proteins, so that binding of a drug to plasma proteins may hinder drug uptake by brain. Plasma protein content and binding can change in aging and disease. P. Robinson developed a mathematical model, based on experimental data, that describes the kinetics of binding to proteins and predicts brain uptake rates of various protein-bound drugs. The model includes association and dissociation rate constants for drug/protein complex. Drug uptake is determined mainly by the dissociation rate constant as compared to brain capillary transit time. The model explains absence or entry of bilirubin into the brain (slow dissociation) but entry of palmitate into brain (rapid dissociation), and contributes to the understanding of kernicterus in the newborn.

3. Brain uptakes of anti-cancer, water-soluble drugs. The pharmacokinetics of melphalan and chlorambucil, two structurally related anticancer drugs, were described in rats. The brain uptake chlorambucil was low, but that of melphalan was greater than expected from its lipid solubility, due to its facilitated transport by the large neutral amino acid carrier at the blood-brain barrier. Brain uptakes of both drugs were nevertheless insufficient for treatment of central nervous system tumors. For these drugs to be centrally effective, their uptake must be enhanced by chemical modification. This work was done by N. Greig.

J. REGULATION OF NEURONAL DEVELOPMENT.

1. Human trisomy 21 (Down syndrome) dorsal root ganglion (DRG) neurons in culture. Experimental conditions were established to culture DRG neurons from fetal tissue of human abortuses, 14-17 weeks old, with and without the Down (trisomy 21) karyotype. Current and voltage clamp recordings were made in 4- to 21-day-old primary cultures. The duration of the action potential was reduced in trisomic neurons, due to faster depolarization and repolarization phases. With voltage clamp, three different potassium currents were demonstrated. Trisomic neurons showed decreased activation time constants for these currents. There are distinct differences in the action potential, and in specific potassium conductances, between trisomy 21 and normal human DRG neurons. This work was done by K. Nieminen.

2. Membrane properties of neurons of trisomy 16 mice. Trisomy 16 in the mouse is a model for trisomy 21 (Down syndrome) in humans, as specific genes on murine chromosome 16 correspond to genes on human chromosome 21 which contribute to the Down phenotype. Experimental conditions were established to culture DRG and spinal cord neurons from fetal trisomy 16 and control mice. Intracellular electrodes were employed to measure electrical membrane properties. Trisomic neurons had a faster rate of rise of the action potential (depolarization), and a faster rate of fall of the action potential (repolarization), than controls, resulting in a shorter overall action potential. Overproduction of products of genes on chromosome 16 in the mouse results in abnormal electrical properties of neurons during development. Furthermore, the action potential abnormality in murine trisomy 16 neurons corresponds to the abnormality in human trisomy 21 neurons. This work was done by C. Orozco.

3. Voltage activated conductances in trisomy 16 neurons. Two sodium conductances, a fast tetrodotoxin (TTX)-sensitive and a slow TTX-resistant conductance, were demonstrated in trisomy 16 and control mouse DRG neurons in culture, using a whole cell patch clamp technique. The slow TTX-resistant conductance was 3-4 times higher than the fast TTX-sensitive conductance, indicating that the action potential of fetal DRG neurons is sustained by the slow conductance. Both conductances were about 50% higher in trisomy 16 than in control neurons, accounting for the higher rate of depolarization of the action potential in trisomic neurons. This work was conducted by C. Orozco.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00120-11 LN

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Blood-Brain Barrier and Central Nervous System Function

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	N.H. Greig	Visiting Associate	LN, NIA
	P.J. Robinson	Senior Staff Fellow	LN, NIA
	S.I. Rapoport	Chief	LN, NIA

Others:	T.T. Soncrant	Senior Staff Fellow	LN, NIA
	H.W. Holloway	Biologist	LN, NIA
	K.M. Wozniak	Visiting Associate	LCS, NIMH
	E.M. Daly	Chemist	LN, NIA

COOPERATING UNITS (if any)

Laboratory of Clinical Sciences, NIMH

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

4.0

PROFESSIONAL:

3.0

OTHER:

1.0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A model was developed to interpret the binding of drugs and physiological substances to plasma proteins to determine how this binding effects the brain uptake of highly bound substances. The model was applied to bilirubin to assess kernicterus in infants.

The blood brain barrier could be opened in rats and mice by intracarotid infusion of a hypertonic arabinose solution. The rate of reclosure was related to the size of the intravascular tracer, indicating that tight junctions between cerebrovascular endothelial cells were modified. Reversible osmotic barrier opening was used to deliver interferon to the brain of rats.

Pharmacokinetic analysis of human interferon-alpha was undertaken in plasma and 7 tissues following intravenous bolus and infusion schedules in rats. The results can be applied to optimize the use of this agent in humans.

The brain uptake and pharmacokinetics of the therapeutic alkylating drugs melphalan and chlorambucil were measured in rats. Brain concentrations of both were minimal and neither is recommended as first-line treatment for intracerebral tumors in humans.

A two dimensional model of vasogenic brain edema was constructed for simulation and prediction of edema in humans as a consequence of disease processes.

IRP-LN-129

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00121-11 LN

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Function and Structure of Peripheral Nerve

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: C. Latker Senior Staff Fellow LN, NIA
K. C. Wadhvani Staff Fellow LN, NIA
J. Koistinaho Visiting Fellow LN, NIA
E. Rechthand Senior Staff Fellow LN, NIA
Q. R. Smith Section Chief LN, NIA

Others: S. I. Rapoport Laboratory Chief LN, NIA
S. Sato Guest Researcher Univ. of Kio

COOPERATING UNITS (if any)

Univ. of Kio, Tokyo; Univ. of Maryland; US Uniformed Health Services, MD;
Univ. of Linkoping, Linkoping, Sweden.

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Neurochemistry and Brain Transport

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

5.0

PROFESSIONAL:

4.0

OTHER:

1.0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Blood-nerve barrier permeability to ions and nonelectrolytes is very low, indicating limited exchange between plasma and nerve endoneurium. The nerve barrier, unlike the brain barrier, does not have regulatory transport systems for potassium and calcium. Nerve concentrations of these ions can change during chronic alterations in plasma concentrations.

Glucose transport across the blood-nerve barrier from plasma to nerve endoneurium is mediated by a facilitated system that demonstrates stereospecificity and saturation, and allows matching of transport and metabolic demand.

Permeabilities of both nerve capillaries and perineurium increase during the first few weeks of Wallerian degeneration. Nerve capillary permeability eventually returns to normal, but perineurial permeability remains elevated, suggesting that nerve fibers are required to maintain the blood-nerve barrier integrity.

Blood flow in the rat sciatic nerve, as measured with laser Doppler flowmetry, increases during hypercapnia, indicating that the vasa nervorum is sensitive to local metabolic conditions.

The localization of alkaline phosphatase to caveolae of frog perineurium and rat endoneurial capillaries indicates that these structures may function as microdomains of enzymatic activity.

IRP-LN-130

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00123-10 LN

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neuronal Development in Tissue Culture

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	B. Ault	Senior Staff Fellow	LN, NIA
	P. Caviedes	Visiting Fellow	LN, NIA
	J. Hidalgo	Visiting Fellow	LN, NIA
	J. Koistinaho	Visiting Fellow	LN, NIA
Others:	J. DeGeorge	Senior Staff Fellow	LN, NIA
	D. Gambal	Guest Researcher	LN, NIA
	K. Nieminen	Visiting Fellow	LN, NIA

COOPERATING UNITS (if any)

Department of Pediatrics, University of California at San Francisco.

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

3.75

PROFESSIONAL:

3.75

OTHER:

0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Dorsal root ganglion (DRG) neurons from fetal trisomy 16 mice, a model for trisomy 21 (Down syndrome) in humans, were shown in tissue culture to have altered electrical properties compared to control neurons. Action potentials of shorter duration with higher rates of depolarization and repolarization were present in the trisomy 16 neurons studied. Similar differences were observed between trisomy 16 and control spinal cord neurons. With voltage clamp recording, a fast tetrodotoxin (TTX)-sensitive and a slow TTX-resistant sodium conductance were examined. Both conductances were elevated in trisomy 16 compared to control neurons.

Cultured human fetal DRG neurons with trisomy 21 had a shorter duration action potential relative to control neurons. Voltage clamp studies revealed a decreased activation time constant for outward potassium currents. A fast TTX-sensitive and a slow TTX-insensitive sodium current could be identified, the latter accounting for 90% of the total charge moving across the membrane. The slow sodium component showed slowed inactivation kinetics, although no difference in maximal conductance was observed.

Binding analyses suggested that the number of sodium channels decreased in trisomy 16 neurons, which also have abnormal lipid metabolism and neurotransmitter uptake.

IRP-LN-131

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00125-10 LN

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cerebral Metabolism, Relation to Brain Function and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	T. Soncrant	Senior Staff Fellow	LN, NIA
	U. Freo	Visiting Fellow	LN, NIA

Others:	H. Holloway	Biologist	LN, NIA
	D. Larson	Biologist	LN, NIA
	K. Wozniak	Visiting Fellow	LCS, NIMH
	D. Murphy	Chief	LCS, NIMH
	D. McNamara	Summer Student	LN, NIA

COOPERATING UNITS (if any)

Department of Neuropathology, Univ. Western Ontario
 Laboratory of Clinical Sciences, NIMH
 Laboratory of Analytical Chemistry, NIDDK

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

5.0

PROFESSIONAL:

3.0

OTHER:

2.0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

The regional cerebral metabolic rate for glucose was measured with the [14C]2-deoxy-D-glucose technique in young and aged male Fischer-344 rats, following administration of cholinergic (arecoline), dopaminergic (haloperidol, bromocriptine), and serotonergic (m-chlorophenylpiperazine) drugs. For arecoline, the absence of age differences in most brain areas indicated that muscarinic receptor mechanisms are intact in the rat brain during aging. Responses to bromocriptine and haloperidol were reduced in senescent as compared to younger rats, suggesting reduced central dopaminergic function, and an imbalance between cholinergic and dopaminergic systems.

Structural analogs of physostigmine, a cholinesterase inhibitor, were synthesized. Some were shown to have longer half-lives and greater selectivity for acetylcholinesterase than does physostigmine.

IRP-LN-132

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00126-09 LN

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Brain Function in Aging and Dementia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	R. Friedland	Chief, BADS	LN, NIA
	C. Grady	Research Psychologist	LN, NIA
	M. Schapiro	Senior Staff Fellow	LN, NIA
	B. Horwitz	Senior Staff Fellow	LN, NIA
	A. Kumar	Medical Staff Fellow	LN, NIA

COOPERATING UNITS (if any)

Child Psychiatry Branch, NIMH;
Department of Nuclear Medicine, CC

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Brain Aging and Dementia Section

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

2

PROFESSIONAL:

2

OTHER:

0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

No significant relation between age at onset of dementia and neuropsychologic manifestations of Alzheimer's disease (AD) was found when early and late onset patients were compared, although early onset patients had more severe parietal hypometabolism. Longitudinal analysis of mildly demented AD patients demonstrated that neuropsychological deficits were preceded by metabolic abnormalities by many months. Using a linear histogram method, ratios of peak cerebral glucose utilization in association cerebral cortex to peak utilization in primary cortex were significantly reduced in mildly and moderately-severe demented AD patients. These ratios correlated significantly with dementia severity. Longitudinal analysis of metabolic asymmetries and language performance in AD patients showed that disproportionate left hemisphere hypometabolism predicted later declines in comprehension and repetition. Patients with obsessive-compulsive disorder were compared to age-matched controls and found to have higher rates of glucose utilization in frontal cortical regions. Those patients who responded favorably to drug therapy had metabolic rates that were closer to normal.

Regional cerebral metabolism was reduced in older as compared to younger adults with Down syndrome, as expected from the Alzheimer-type neuropathology in older Down subjects. Similarities between Alzheimer's disease and dementia and cognitive deterioration in Down syndrome were demonstrated.

A phylogenetic hypothesis for Alzheimer's disease (and Down syndrome) was proposed, based on evidence that both diseases affect the function and metabolism of the association as compared to primary sensory and motor neocortices early and throughout their courses.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00127-08 LN

PERIOD COVERED

October 1, 1987 To September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neurochemistry of the Nervous System in Aging and Neurodegenerative Disorders

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	J. Atack	Visiting Associate	LN, NIA
	G. Yang	Visiting Fellow	LN, NIA
Others:	M. Matocha	Staff Fellow	LN, NIA
	C. Franco-Hidalgo	Visiting Fellow	LN, NIA
	M. Bitar	Staff Fellow	LN, NIA
	G. Wenk	Neurochemist	Johns Hopkins
	D. Katz	Pathologist	CC, NIH

COOPERATING UNITS (if any)

Department of Behavioral Sciences, Johns Hopkins Medical School, Baltimore
 Dept. of Neuropathology, Univ. Western Ontario, Canada. Dept. of Pathology,
 CC, NIH, Dept. of Pathology, Miriam Hospital, Brown Univ., Providence, RI

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

2.5

PROFESSIONAL:

2.5

OTHER:

0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Following a unilateral lesion of the rat nucleus basalis of Meynert, there was an acute (1 week) increase in the number of neocortical M2 muscarinic binding sites which returned to normal after 3 months. Neocortical M1 muscarinic binding sites were normal at 1 week but decreased at 3 months. These changes were bilateral and suggest that bilateral changes in cortical cholinergic receptors follow unilateral degeneration of cholinergic input.

The differentiation of adrenergic derivatives of the rat neural crest was examined using the glucocorticoid receptor (GR) as the molecular marker. Both adrenal and extra-adrenal chromaffin cells were found to have similar temporal patterns of GR localization and responsiveness to dexamethasone during postnatal development, while these same characteristics were not found in sympathetic neurons. In streptozotocin (STZ)-treated diabetic rats, adrenal tyrosine hydroxylase (TH), dopamine beta-hydroxylase (DBH) and phenylethanolamine N-methyltransferase (PNMT) activities were all increased as were concentrations of dopamine, norepinephrine and epinephrine. Binding of [3H]prazosin and [3H]dihydroalprenolol to myocardial adrenergic receptors were decreased. These results suggest that catecholaminergic abnormalities may contribute to metabolic deficits in diabetes mellitus.

Nerve growth factor (NGF) receptors were identified in the human cerebral cortex and had a dissociation constant (Kd) of 150-300 pM. The binding of [125I]-NGF to membranes prepared from Alzheimer's disease brains did not differ significantly from binding in normal brains.

Immunocytochemistry with polyclonal antibodies, demonstrated for plasma proteins in normal formalin-fixed brain tissue in a number of subcortical regions, including the nucleus basalis, thalamus, hypothalamus, dentate nucleus and spinal cord. Only a few pyramidal neurons in cortical layers III and V were positive.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00128-08 LN

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Analytical Drug Methods

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	T. Soncrant	Sr. Staff Fellow	LN, NIA
	N. Greig	Visiting Associate	LN, NIA

Others:	E. Daly	Chemist	LN, NIA
	G. Phelan	IRTA Fellow	LN, NIA
	M. Backus	Chemist	LN, NIA
	D. Sweeney	Chemist	LN, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

An analytical method using high performance liquid chromatography with ultraviolet detection was developed for the measurement of bromocriptine, a dopaminergic agonist, in plasma and brain of rats.

IRP-LN-135

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00129-08 LN

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Brain Nutrients and Metals in Aging and Disease

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Q. R. Smith	Section Chief	LN, NIA
	V. Murphy	Senior Staff Fellow	LN, NIA
	S. Fukui	Visiting Fellow	LN, NIA
	H. Mori	Visiting Fellow	LN, NIA
Others:	S. I. Rapoport	Laboratory Chief	LN, NIA
	B. W. Agranoff	Professor	Univ. of Michigan

COOPERATING UNITS (if any)

Univ. of Michigan, MI; Unit on Neurotoxicology, INSERM, Paris, France; Oak Ridge Associated Universities, TN; Tokyo Medical and Dental University, Tokyo, Japan.

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Neurochemistry and Brain Transport

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

4.0

PROFESSIONAL:

4.0

OTHER:

0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

Neutral amino acids are taken up from plasma into brain by a single high-affinity transport system at brain capillaries. Transport affinity differs among neutral amino acids by 700 fold and is determined primarily by amino acid side chain hydrophobicity. At normal plasma concentrations the transport system is saturated, forcing individual amino acid to compete for available transport sites. Competition makes the brain susceptible to imbalances in plasma concentrations.

Neutral amino acid transport into rat brain decreases between 1 week and 3 months of age and then remains constant between 3 and 24 months. Changes in amino acid transport with development and aging correlate with changes in brain protein synthesis.

The nonmetabolizable amino acid, 1-aminocyclohexanecarboxylic acid, is transported by the cerebrovascular neutral amino acid carrier and may be a suitable in vivo probe of amino acid transport in humans using positron emission tomography.

Calcium influx into cerebrospinal fluid is maintained constant during chronic hypocalcemia by saturable, Vitamin D-independent transport at the choroid plexus epithelium. In contrast, calcium transport across brain capillaries may not be regulated during hypocalcemia.

An electron beam X-ray microanalysis method was developed to determine metal concentrations in human brain tissue. Analysis of samples from patients with Alzheimer's disease demonstrated that aluminum is not accumulated significantly in senile plaques as compared to surrounding brain tissue.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00130-06 LN

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neuropsychological Function in Aging and Dementia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	J. V. Haxby	Unit Chief, Neuropsychology	LN, NIA
	C. L. Grady	Research Psychologist	LN, NIA
	E. Koss	Senior Staff Fellow	LN, NIA
Others:	B. Sones	Speech Pathologist	RM, CC
	R. Parasuraman	Cognitive Psychologist	Catholic Univ.
	J. Heisey	Psychologist	LN, NIA
	P. Nestor	Psychologist	Catholic Univ.

COOPERATING UNITS (if any)

Rehabilitation Medicine Department, Clinical Center;
Department of Psychology, Catholic University, Washington, D.C.

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Brain Aging and Dementia Section

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

2

PROFESSIONAL:

2

OTHER:

0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Neuropsychologically relevant mental abilities are studied in healthy men at different ages, in patients with clinically-diagnosed Alzheimer's disease, and in adults with Down syndrome at different ages. Tests are administered to evaluate intelligence, memory, language, visual attention, visuo-perceptive and visuoconstructive ability, and perceptual-motor speed. The presence and neuroanatomical location of separate visual pathways for spatial vision and object vision were demonstrated in healthy young men by measuring regional cerebral blood flow (rCBF) with positron emission tomography (PET) and H-2-15-0. Age-related differences on verbal processing and memory were not statistically significant in our sample of healthy men, ranging in age from 20 to 83 years, whereas, age-related differences on visuospatial processing and memory were significant but smaller than differences reported for non-health-screened adults. In healthy adults, visual memory and the discrepancy between verbal and visuospatial ability were not correlated with regional cerebral metabolic rates for glucose (rCMRglc) as measured by PET and 18-Fluorodeoxyglucose, but the discrepancy between visual and verbal memory was correlated with right-left parietal rCMRglc asymmetry. Neuropsychological patterns were correlated with neocortical rCMRglc patterns in patients with moderate Alzheimer's disease, but not in patients with mild Alzheimer's disease. Longitudinal study of mildly impaired patients, however, demonstrated that the development of neocortically-mediated neuropsychological impairments follows the appearance of significant neocortical rCMRglc abnormalities. Older Down syndrome adults without clinically significant dementia perform worse on memory and visuospatial construction tests than do younger subjects.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00131-06 LN

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neurological Function in Aging and Dementia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal investigator) (Name, title, laboratory, and institute affiliation)

P.I.:	C. Grady	Research Psychologist	LN, NIA
	J. Kaye	Medical Staff Fellow	LN, NIA
Others:	A. Grimes	Audiologist	CC
	A. Pikus	Audiologist	CC
	J. W. Renfrew	Psychologist	LN, NIA
	C. May	Medical Staff Fellow	LN, NIA
	M. Shapiro	Senior Staff Fellow	LN, NIA
	R. Friedland	Chief, BADS	LN, NIA

COOPERATING UNITS (if any)

Audiology, CC

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Brain Aging and Dementia Section

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS

.8

PROFESSIONAL

.5

OTHER

.3

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

Research was carried out on motor function in man in relation to aging. With the use of a patient activity monitor worn on the non-dominant wrist in 43 healthy men for a period of 9 days, it was demonstrated that average motor activity was lower in older individuals, primarily as a result of low activity during daytime hours. Weekend mean activity was significantly different than weekday mean activity only in the younger subjects as a result of young subjects sleeping later on weekends than during the weekday period. The monitor was shown to be useful in quantifying nocturnal disturbances, such as wandering, in patients with Alzheimer's disease.

In patients with Alzheimer's disease, studies of central auditory function using both dichotic and degraded monotic tests showed that performance on the dichotic test was more difficult for the patients, compared to healthy controls. Only dichotic performance was related to measures of cerebral atrophy and glucose metabolism in the temporal lobes. Evoked potential latencies were not different in patients with Alzheimer's disease compared to controls.

Basal metabolic rate (BMR) was measured in young subjects with Down Syndrome (DS) and healthy controls to see if extra genomic material affects basal metabolism. No difference was found between DS subjects and controls, suggesting that chromosome 21 does not control BMR.

The occurrence of motor vehicle accidents was assessed in patients with Alzheimer's disease to determine the effect of cognitive deterioration on the complex motor behavior of driving. Patients were found to have more accidents than elderly controls (47 percent versus 10 percent), but these were not related to disease severity or duration.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00132-06 LN

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Brain Anatomy in Aging and Dementia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	C. DeCarli	Medical Staff Fellow	LN, NIA
	B. Horwitz	Senior Staff Fellow	LN, NIA
	J. Kaye	Medical Staff Fellow	LN, NIA
Others:	R. Friedland	Chief, BADS	LN, NIA
	J. Luxenberg	Medical Staff Fellow	LN, NIA
	S.I. Rapoport	Chief	LN, NIA
	L. Levy	Guest Researcher	NIS, NINCDS

COOPERATING UNITS (if any)

LNC, NIMH, NIH; NIS, NINCDS, NIH; CC Radiology, NIH

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Brain Aging and Dementia Section

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

1.6

PROFESSIONAL:

1.6

OTHER:

0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The transverse computer assisted tomography (CT) method of calculating ventricular volumes of the human brain in vivo, using TRACE image analysis, procedure was found to be highly reliable, and suitable for longitudinal studies of aging and dementia.

Quantitative CT analyses in healthy aging men and women demonstrated significant sex differences in ventricular volume and in age of onset of ventricular enlargement. Structural brain changes, as measured by ventricular enlargement, and decline in cognitive performance on the WAIS appear to be relatively independent processes correlated more to the age of the subject. Future studies using magnetic resonance imaging (MRI) will be devoted to analyzing other structures which may change with age and explain the mild cognitive decline seen in healthy aging, and will form the basis for comparison to patients with dementia of the Alzheimer's type (DAT).

Three sets of monozygotic twins discordant for DAT were studied and found to have significant differences in cross sectional ventricular volumes. Moreover, the DAT patients were found to have greater than two standard deviation increased rates of ventricular enlargement whereas their unaffected twins were within the normal range. Down syndrome (DS) patients with dementia were also shown to have a significantly increased rate of ventricular enlargement when compared to young and nondemented older DS patients.

NOTICE OF INTRAMURAL RESEARCH PROJECT

201 AG 01135-06 LN

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Clinical Pharmacokinetics, Pharmacodynamics and Therapeutics

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory and institute affiliation)

PI: J. Kaye Medical Staff Fellow LN, NIA

Others: C. May Medical Staff Fellow LN, NIA

T. Soncrant Senior Staff Fellow LN, NIA

A. Kumar Medical Staff Fellow LN, NIA

C. DeCarli Medical Staff Fellow LN, NIA

S. Kaufman Chief, Laboratory of
Neurochemistry NIMH

COOPERATING UNITS (if any)

Laboratory of Neurochemistry, NIMH;

Section of Clinical Psychopharmacology, NIMH;

Office of Scientific Director, NINCDS; Human Motor Control Section, NINCDS

College of Pharmacy, University of Saskatchewan, Canada

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Brain Aging and Dementia

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS

1

PROFESSIONAL

1

OTHER

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Subcutaneous tetrahydrobiopterin (a cofactor in monoamine synthesis) was administered to 5 patients with dementia of the Alzheimer type. No gross change in neurologic examination or significant adverse effects were observed. Cerebrospinal fluid (CSF) drug and monoamine metabolite concentrations were evaluated.

Intravenous haloperidol (a dopaminergic antagonist) was administered to 5 healthy subjects to test the dopamine system in aging. No significant adverse effects were seen. Plasma haloperidol and prolactin concentrations and quantitative cognitive and motor tests were evaluated.

Oral debrisoquin was administered to 9 healthy subjects to assess central nervous system dopamine activity in relation to aging. Adverse effects were recorded (nausea, anorexia) in 1 patient. Plasma and urine monoamine metabolites will be analyzed.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00134-05 LN

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Brain Lipid Metabolism, Relation to Function and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: J. Gnaedinger Noronha Senior Staff Fellow LN, NIA
J. DeGeorge Senior Staff Fellow LN, NIA

Others: S. Yamazaki Visiting Fellow LN, NIA
P. Robinson Senior Staff Fellow LN, NIA
J. Miller Staff Fellow LN, NIA
O. Tone Visiting Fellow LN, NIA
J. Bell Chemist LN, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

4.75

PROFESSIONAL:

3.50

OTHER:

1.25

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A method was developed to measure the rate of incorporation of palmitate, Jpalm, from plasma into different brain regions in the awake rat. A theoretical model was developed to calculate Jpalm from data.

The distribution of [14C]palmitate in biochemically separated brain fractions indicated that the radioactivity being measured in the autoradiograms is predominantly in lipid molecules found in membranes. Phosphatidyl choline contains the greatest amount of total lipid label.

Jpalm did not change with aging in Fischer-344 rats between 3 and 34 months of age, indicating that the rate of turnover of palmitate-containing brain lipids was age-invariant.

Jpalm was reduced in central auditory pathways following chronic damage to the cochlea. Several days following a 5-minute period of bilateral ischemia, gerbils had reduced palmitate incorporation into the irreversibly damaged CA1 region of the hippocampus but increased incorporation into recovering regions such as the CA3 and dentate gyrus.

Palmitate incorporation into the hypoglossal nucleus increased maximally 24 days after hypoglossal nerve axotomy. This increase correlated with nerve regeneration. Following axotomies in which regeneration was prevented, palmitate incorporation remained decreased between 24 and 35 days.

IRP-LN-141

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00135-05 LN

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Molecular Biology of Brain Aging and Disease

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: M. Matocha Staff Fellow LN, NIA

Others: J.R. Atack Visiting Associate LN, NIA

J.W. Cosgrove Senior Staff Fellow NINCDS

G. Yang Visiting Fellow LN, NIA

C. Chandrasekaran Visiting Scientist LN, NIA

COOPERATING UNITS (if any)

National Institute of Neurological and Communicative Disorders and Stroke

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

2.25

PROFESSIONAL:

2.25

OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Differential gene expression in the rat brain at the level of protein end-product was observed for a number of brain proteins, but the level of most brain proteins did not change with age. Differential gene expression also was observed for a number of brain mRNAs, but the majority did not change with age.

The expression of the c-fos, c-myc and c-myb nuclear related oncogenes was examined in the rat brain. Sequences related to c-fos and c-myc but not to c-myb were detected. The expression of these sequences did not change with aging. In addition, the levels of B-actin mRNA did not change with age.

Transcript levels of several proto-oncogenes were measured in brain and liver of rats by Northern blot hybridization analysis. An age-related increase in the level of c-myc mRNA in liver, but not brain, was observed. The levels of B-actin, c-sis, and c-src-related transcripts were age-invariant in both organs.

The pp60c-src specific activity were measured in whole brain of Fischer-344 rats in an in vitro immune complex kinase assay. There was no significant difference in the pp60c-src specific kinase activity as a function of age.

In situ hybridization methods were developed to measure the cellular levels of genes involved in cell signaling mechanisms. High levels of expression of c-myc and the glucocorticoid receptor (GR) genes were found in rat brain. Quantitative analysis indicated that the levels of GR transcripts were significantly different between contiguous but neuroanatomically-distinct regions of the hippocampus.

IRP-LN-142

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00140-04 LN

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cerebrospinal Fluid Chemistry in Aging and Dementia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	C. May	Medical Staff Fellow	LN, NIA
	J.A. Kaye	Medical Staff Fellow	LN, NIA
	S.I. Rapoport	Chief	LN, NIA
Others:	J.R. Atack	Visiting Associate	LN, NIA
	J. DeGeorge	Senior Staff Fellow	LN, NIA
	I. Rainero	Guest Worker	LN, NIA
	M.B. Schapiro	Senior Staff Fellow	LN, NIA

COOPERATING UNITS (if any)

Laboratory of Neurochemistry, NIMH; Department of Pharmacology and Experimental Therapeutics, Loyola University; Department of Neurology, Massachusetts General Hospital, Boston

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Brain Aging and Dementia Section/Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

1.4

PROFESSIONAL:

1.4

OTHER

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Emphasis has been placed on the identification of subtypes of dementia of the Alzheimer type (DAT) - DAT with motor abnormalities, such as extrapyramidal signs (EDAT) and myoclonus (MDAT); DAT of early- (less than 65 yr) and late-onset (greater than 65 yr), using neurochemical measurements in the cerebrospinal fluid (CSF). The reductions in somatostatin-like immunoreactivity (SLI) and acetylcholinesterase (AChE) activity found in DAT are also present in EDAT and MDAT. In addition, the latter groups have deficits in the monoaminergic neurotransmitter systems. EDAT and MDAT patients have reduced CSF concentrations of homovanillic acid (HVA) and the hydroxylation cofactor biopterin; MDAT patients also have reductions in CSF 5-hydroxy-indoleacetic acid (5-HIAA). Compared to age-matched control subjects, early-onset DAT patients have reductions in CSF AChE activity, and late-onset DAT patients have reductions in CSF alpha-melanocyte stimulating hormone-like immunoreactivity (alpha-MSH-LI).

An inverse relation between CSF HVA and alpha-MSH-LI was found in the DAT patient group. Furthermore, in patients with Parkinson's disease (who are known to have abnormalities of the dopaminergic system), CSF alpha-MSH-LI was found to be elevated. Young subjects with Down's syndrome have higher levels of CSF choline, 5-HIAA and norepinephrine than age-matched control subjects. In healthy control subjects, age-related increases were found in CSF total protein, choline, the polyols erythritol and myoinositol, and AChE activity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00400-04 LN

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cellular Mechanisms of Blood Vessels Regression

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Principal Investigator has transferred to another Institute.

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

0

PROFESSIONAL:

0

OTHER:

0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Project terminated 1987.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00403-03 LN

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less Title must fit on one line between the borders)

Genetics of Alzheimer's Disease

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I.: Angela M. Moore	Social Worker	LN, NIA
Mark Schapiro	Senior Staff Fellow	LN, NIA
Anand Kumar	Medical Staff Fellow	LN, NIA
Others: Beverly White	Medical Research Fellow	LCB, NIDDK
Katherine K. Sanford	Chief, In Vitro Carcinogenic Section	LCMB, NCI
Ram Parshad	Professor, Dept. of Pathology	Howard University
George Zubenko	Associate Professor	Univ. of Pittsburgh

COOPERATING UNITS (if any)

LCB, NIDDK, NIH; LCMB, NCI, NIH;
Howard University, Washington, D.C.;
University of Pittsburgh

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Brain Aging and Dementia Section

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS

.5

PROFESSIONAL:

.2

OTHER

.3

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Pedigrees were constructed from the family histories of all patients participating in the dementia program in order to examine the genetic basis of Alzheimer's disease.

Collaborative studies were established to examine the ability of peripheral blood lymphocytes of probands with Down syndrome and familial Alzheimer's disease to repair X-irradiation induced damage during the G2 period of the cell cycle, and for the Down syndrome subjects, to see if the parents' lymphocytes show chromosomal instability.

Efforts continue to evaluate genetic aspects of presenile dementia. Specifically, secondary sex chromosomal variation, alpha-1-antitrypsin (PI) phenotyping, and cytological analysis of variations in the Nucleolus Organizing Regions (NOR) were analyzed.

Collaborative studies were established to address the questions of platelet membrane fluidity in Alzheimer's disease.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00404-02 LN

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Functional Interactions Among Brain Regions in Aging and Dementia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: B. Horwitz Senior Staff Fellow LN, NIA

Others: T. Soncrant Senior Staff Fellow LN, NIA
 C. L. Grady Research Psychologist LN, NIA
 J. Rumsey Senior Staff Fellow CHP, NIMH
 M. B. Schapiro Senior Staff Fellow LN, NIA
 J. V. Haxby Senior Staff Fellow LN, NIA
 S. Sato Visiting Fellow LN, NIA

COOPERATING UNITS (if any)

Child Psychiatry Branch, NIMH

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

.75

PROFESSIONAL:

.75

OTHER:

0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

A matrix method was developed to examine functional interactions between brain regions, by correlating regional cerebral metabolic rates for glucose determined by positron emission tomography in humans. The method was applied to data from 14 autistic patients and 14 age- and sex-matched controls. Compared with controls, the autistic group had significantly fewer large correlations between pairs of regions in the frontal and parietal lobes, and between subcortical nuclei and frontal/parietal regions. These results are consistent with the view that autism represents a dysfunction in neural systems associated with directed attention. The correlation method also was applied to data from 14 young adult patients with Down Syndrome and 24 matched control subjects. Compared with controls, the Down Syndrome group had many correlations within and between the frontal and parietal lobes with lower values, and many correlations between the thalamus and cortex with reduced values. These results also indicate a disruption of neural systems associated with attention in Down Syndrome.

The matrix method was applied to data from awake Fischer-344 rats. Reduced correlations between left and right hemispheric brain regions were found in rats that had undergone corpus callosotomies, suggesting that interhemispheric interactions are mediated in part by callosal fibers.

A neurobiological hypothesis was proposed to explain the relation between the percentage cell loss in the cholinergic basal forebrain and the density of neuritic plaques in cortex in Alzheimer's disease: When cells in the cholinergic basal forebrain die, their cortical synaptic target sites can be reoccupied by axonal sprouting of other neurons from the basal forebrain. This neuroplasticity hypothesis leads to equations that are consistent with the quantitative data, and makes specific testable predictions. This hypothesis suggests that the more rapid course of the presenile form of Alzheimer's disease and its more extensive pathology can be understood as a consequence of the decline in neuroplasticity with age.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00405-02 LN

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

New Investigations in Aging and Dementia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I.:	R. Friedland	Chief, BADS	LN, NIA
	A. Kumar	Medical Staff Fellow	LN, NIA
	S. I. Rapoport	Chief	LN, NIA
	C. DeCarli	Medical Staff Fellow	LN, NIA
	M. Schapiro	Senior Staff Fellow	LN, NIA

Other:	F. Boller	Prof., Neurology	Univ. of Pittsburgh
	C. Reynolds	Prof., Psychiatry	Univ. of Pittsburgh

COOPERATING UNITS (if any)

University of Pittsburgh, Department of Neurology and Psychiatry, Pittsburgh
University of Colorado, School of Medicine, Denver
Duke University, Durham, NC

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Brain Aging and Dementia Section

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

2.0

PROFESSIONAL:

2.0

OTHER:

0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

A number of new protocols were introduced to examine brain aging and cerebral metabolism. In using the isotope fluoro-18-deoxyglucose with positron emission tomography, we found that cerebral glucose utilization does not change with advancing age in healthy males, but changes are found in patients with Alzheimer's disease and Down syndrome. Four new protocols allow us to evaluate these findings and determine their specificity. Studies are underway in multi-infarct dementia, the second leading cause of dementia; a major depressive disorder both with and without cognitive impairment; and fragile-X syndrome to evaluate PET alterations uncovered in our laboratory in subjects with Down syndrome. We also are studying healthy adult subjects with hypertension who have no symptomatic cognitive impairment.

Annual Report of the Laboratory of Personality and Cognition

National Institute on Aging

Overview

The fundamental scientific paradigm which unites and guides research in the Laboratory of Personality and Cognition is the analysis of individual differences. Few phenomena are more basic than the fact that human beings differ--in health, in rates of aging, in cognitive ability, in personality, in happiness and life satisfaction. The mission of the LPC is threefold: (1) to conduct basic and clinical research on individual differences in cognitive and personality processes and traits; (2) to investigate the influence of age on these variables and their reciprocal influence on health, well-being, and adaptation; and (3) to employ longitudinal, experimental, and epidemiological methods in the analysis of psychological and psychosocial issues of aging including health and illness, predictors of intellectual competence and decline, models of adult personality, and correlates of disease risk factors.

Research Activities

This was another productive and exciting year for the Laboratory of Personality and Cognition. In the area of health and aging, the Laboratory has been involved in successful reanalyses of the MRFIT study pointing toward the importance of Agreeableness-antagonism as a possible predictor of Coronary Heart Disease (CHD). LPC researchers also confirmed earlier studies on the absence of an association between Neuroticism and CHD in a 10-year prospective study of a national probability sample of over 5000 adults.

Basic research in personality structure has also progressed, marked by an integration of two important research traditions: the five-factor model and the interpersonal circumplex. The growing importance of the five-factor model to the field of personality assessment as a whole was made clear at a recent conference on "Emerging Issues in Personality Psychology" held at the University of Michigan, in which the work of this Laboratory was ably represented by Dr. Robert McCrae. International interest in the taxonomic model has been shown by recent invitations to conferences in Sydney, Australia (XXIV Intl. Congress of Psychology), Groningen, The Netherlands (Invited Workshop on Personality Language), Jyväskylä, Finland (Intl. Society for the Study of Behavior Development) and Jerusalem, Israel (1st Intl. Symposium on Heart Failure).

Researchers in the Cognition section, under the experienced leadership of Dr. Arenberg, have continued their long-term collection of longitudinal data on many facets of cognitive performance. Dr. Giambra's new emphases on attentional processes importantly augment this rich archive. In recent years, particular attention has been paid to the possible confounding role of health status variables such as Diabetes Mellitus, hypertension and glucose regulation.

The topic of aging and personality has been central to the mission of the PSC Section since its inception. This year the chief of that section was invited to deliver a Master Lecture on "Personality Continuity and the Changes of Adult Life" by the American Psychological Association at their annual scientific meetings in Atlanta. The lecture draws on the empirical studies that have been conducted in the LPC and elsewhere, and, in addition, points to possible new directions for research, including the study of personality changes in the first decade of adulthood, 20-30, and the contributions of personality stability to a new psychology of adulthood.

In May, the Laboratory of Personality and Cognition underwent an intensive review by the Board of Scientific Counselors. Preliminary feedback suggested that the scientific programs of the Laboratory were well received. Scientists in the Laboratory look forward to receiving the suggestions and recommendations that the Scientific Counselors will be making.

Research Training and Collaborations

In addition to its broad program of research, LPC is extremely active in providing an array of training opportunities ranging from undergraduate and graduate research practica to formal pre- and post-doctoral training fellowship opportunities. Recently, LPC became an approved pre-doctoral internship site for the Ph.D. program in Psychobiology/Behavioral Medicine of the University of Maryland, Baltimore County. LPC is able to offer its interns unique opportunities to gain research training and expertise in the analysis of large multivariate data sets, including the longitudinal data archives of the BLSA and the National Health and Nutrition Epidemiologic Survey (NHANES). A major goal is for the interns to acquire skills not only in experimental methodology, but also in longitudinal and epidemiological analyses appropriate to prospective studies. In addition to their other duties, interns are expected to conceive of and pursue research projects germane to aging and behavioral medicine; they are supervised by senior scientists in these endeavors, but considerable emphasis is placed on independent scholarship.

Related to the topic of training, it is with pride that we acknowledge the awards garnered by Stephanie V. Stone, a research assistant in the Personality Stress and Coping section, LPC, and a Ph.D. graduate student in psychology at UMBC. Ms. Stone's master's thesis research on gender differences in cardiovascular reactivity was presented as a poster presentation and won a first place at the Graduate Student Research Day, University of Maryland, and also first place at the 1988 annual meeting of the Maryland Psychological Association. In addition, her poster presentation was accepted by the Health Psychology Division (38) of the American Psychological Association and will be presented at the Annual Scientific Meetings in Atlanta, in August 1988.

LPC has two IRTA positions. Dr. Paul Mullen, a recent Ph.D. recipient from Johns Hopkins University, joined the Cognition Section in July of 1988. The PSC Section has also received many fine applications and hopes

a young Ph.D. personality psychologist into the Lab beginning next fiscal year.

Beginning January 1989, Dr. Linda Dougherty, an academic clinical geropsychologist and an Assistant Professor of Psychiatry and Behavioral Sciences at the Medical College of Virginia will join LPC as a postdoctoral fellow. Dr. Dougherty was awarded an NIMH Faculty Scholar Award in Geriatric Mental Health by the Center for the Study of Aging and Mental Health that will provide support for three years to receive training in personality assessment and research under the research preceptorship of the chief, LPC. Also, Dr. Claudia Kawas of the Neurology Department, FSKMC, joins the Laboratory as a Guest Researcher and collaborator on an important study of early markers of Alzheimer's. Dr. Kawas has performed neurological examinations and administered a large battery of neuropsychological measures to over 180 BLSA participants over age 70. Dr. Kawas will work closely with LPC investigators to analyze her data set and relate it to the archival personality and cognitive data of the LPC.

Finally, Dr. Catherine Busch, who is finishing her 5th year as a Staff Fellow in the Section on Personality, Stress and Coping, LPC, has been selected to receive post-doctoral training in a special program on clinical psychology and research at George Washington University. Dr. Busch's expertise in personality structure and assessment made her an ideal candidate for this program. Her research presence in the LPC, especially in the areas of personality assessment utilizing the California Q-sort and longitudinal readministrations of the GZTS, will be sorely missed.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00062-15 LPC

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Aging Influences on Sustained Attention and Task-Unrelated Images and Thoughts

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: L. M. Giambra, Ph.D.	Senior Investigator	LPC, GRC, NIA
D. A. Sack, M.D.	Chief of Inpatient Services	CPB, NIMH
S. Caspar, M.D.	Guest Researcher	CPB, NIMH

COOPERATING UNITS (if any)

Cognitive Sciences Laboratory, Catholic University, Washington, D.C.
Laboratory of Human Performance and Cognitive Studies, ARC, NIDA

LAB/BRANCH

Laboratory of Personality and Cognition

SECTION

Cognition Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

3.85

PROFESSIONAL:

1.8

OTHER:

2.05

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This work attempts to determine the parameters of task-unrelated images and thoughts (TUITs, daydreaming/mindwandering) as well as related mental activity such as insight, attention and sustained attention as phenomena, their relationships amongst one another, and their susceptibility to the influence of aging in adulthood. These goals are accomplished through the use of controlled laboratory studies and retrospective questionnaires. This year's findings were: (a) TUIT frequency during reading is inversely related to subject interest in the material, (b) TUIT frequency shows a circadian variation with a minimum about midnight and a maximum at about 10 am, (c) longitudinal decreases over 7 years in daydreaming frequency as measured by retrospective questionnaire, and (d) extended practice on a high event vigilance task, with typical exposure times, does not reduce or eliminate age decrements in performance.

Former Project Title: Aging Influences On Sustained Attention and Task-Unrelated-Thought-Intrusions

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00064-27 LPC

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Problem Solving and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: D. Arenberg Chief, Cognition Section LPC, NIA

Others: L. M. Giambra Senior Investigator LPC, NIA

COOPERATING UNITS (if any)

Department of Human Development, University of Maryland, College Park
Applied Physiology Section LCP, NIA (J. D. Tobin)

LAB/BRANCH

Laboratory of Personality and Cognition

SECTION

Cognition Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

.7

PROFESSIONAL:

.2

OTHER:

.5

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Among the goals of this project are to describe age differences and changes in reasoning performance and to investigate processes underlying such age-related performance. Last year, concept problem solving, a measure of abstract reasoning, was one of many measures included in analyses relating cognitive performance to glucose tolerance in the women in the Baltimore Longitudinal Study of Aging (BLSA). When age, education, and obesity were taken into account, only concept problem solving was related to the concentration of glucose in the blood two hours after ingestion of a glucose load. Further analyses were carried out for the women in the BLSA who were in their sixties and for those who were over 70. For the women who were in their sixties, better glucose regulation was associated with higher problem solving performance. When only the healthier women in their sixties were included, however, the relationship was substantially reduced. For the women over 70, problem solving performance was not related to the glucose tolerance measure either for the entire group or for the healthier subgroup. Among the women in the BLSA, evidence that glucose regulation affects abstract reasoning in the elderly is weak and inconsistent.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00065-28 LPC

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Verbal Learning and Age

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: D. Arenberg Chief, Cognition Section LPC, NIA

Others: L. M. Giambra Senior Investigator LPC, NIA

P. Mullin IRTA Fellow (EOD 7-1-88) LPC, NIA

COOPERATING UNITS (if any)

Department of Human Development, University of Maryland, College Park
Applied Physiology Section LCP, NIA (J. D. Tobin)

LAB/BRANCH

Laboratory of Personality and Cognition

SECTION

Cognition Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

3.35

PROFESSIONAL:

.85

OTHER:

2.5

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Among the goals of this project are to describe adult age differences and changes in memory and learning performance and to investigate processes underlying such age-related performance. Several measures of memory and information processing known to be age related cross-sectionally were introduced into the Baltimore Longitudinal Study of Aging in 1978. Six-year repeat data are now available for more than 200 men. Almost all of the measures of individual change in immediate and delayed memory of words, memory for digit sequences, simple reaction time, and speed and accuracy of decisions were related to age. The younger men tended to improve slightly and the older men tended to decline.

The literature on verbal learning and aging is substantial and the findings are unequivocal; the performance of young adults is superior to that of older groups. Forgetting of newly learned verbal material has not been studied nearly so extensively, however, and the findings are inconsistent. Two age studies of sentence learning and forgetting were completed in this Laboratory this year. When young and older adults were given the same opportunity to learn many sentences, the typical age differences were found in learning; furthermore, the age differences were maintained 3, 6, and 24 hours after learning. The amount of forgetting was equivalent for the two age groups. When an older group was given more time to study each sentence, learning was equivalent for the two age groups; and the older group did not forget more than the young 3, 6, and 24 hours after learning. These studies provide further evidence that, for newly learned verbal material that is not mastered, forgetting is not age related.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00066-27 LPC

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Perceptual Retention and Age

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: D. Arenberg

Chief, Cognition Section

LPC, NIA

COOPERATING UNITS (if any)

Department of Human Development, University of Maryland, College Park

LAB/BRANCH

Laboratory of Personality and Cognition

SECTION

Cognition Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

.6

PROFESSIONAL:

.2

OTHER:

.4

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A primary goal of this project is to describe adult age differences and age changes in nonverbal memory performance. Nonverbal memory is measured in the Baltimore Longitudinal Study of Aging (BLSA) with the Benton Visual Retention Test (BVRT), a test of memory for designs involving spatial memory. Spatial ability is one of the few aspects of cognitive performance in which gender differences favoring males have been reported frequently for children and young adults. When education was not taken into account in the analysis, comparisons of BVRT performance of men and women across the adult age span favored the men. However, when participants with and without a college degree were analyzed separately, no gender difference was found.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00080-3 LPC

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Age Effects On Automatic and Effortful Information Processing

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: L. M. Giambra, Ph.D. Senior Investigator LPC, GRC, NIA

COOPERATING UNITS (if any)

Human Factors Laboratory, School of Psychology, Georgia Institute of Technology

LAB/BRANCH

Laboratory of Personality and Cognition

SECTION

Cognition Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

.4

PROFESSIONAL:

.1

OTHER:

.3

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of this research is to examine the influence of aging upon the development and enactment of automatic and effortful attentional processes. The purpose is accomplished through controlled laboratory studies. Previous research in this laboratory, investigating the development of automatic visual detection in young, middle-aged, and old adults, found old adults unable to attain automatic detection after extensive practice. An additional series of experiments established that the older adults' failure to develop automatic detection was not due to the nature of the items to be detected, insufficient practice, the practice schedule, or response competition. Automatic detection is viewed as the result of a second level of learning, "priority" learning. The future course of this project will be an examination of the extent to which old adults can go beyond the first level of learning, i.e., "associative" learning, to priority learning which establishes a direct and immediate response of the attentional system to the item to be detected.

The significance of this project lies in mapping out and accounting for maturational changes in the development of automatic visual detection which plays such an important part in our daily lives.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00182-2 LPC

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Age Effects On Concentration During Information Processing

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: L. M. Giambra, Ph.D.	Senior Investigator	LPC, GRC, NIA
R. Barr, Ph.D.	Expert	BSRP, NIA
E. J. Metter, M.D.	Medical Officer	LSB, GRC, NIA

COOPERATING UNITS (if any)

Behavioral Science Research Program, NIA
Longitudinal Studies Branch, IRP, NIA

LAB/BRANCH

Laboratory of Personality and Cognition

SECTION

Cognition Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

.3

PROFESSIONAL:

.1

OTHER:

.2

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A primary purpose of this work is to investigate the relationship between age and concentrative ability. Using laboratory studies of task-unrelated imagery and thought (TUIT) it was determined that old adults had fewer TUITs than young and middle-aged adults. One possible explanation for this result is that age and concentrative ability are directly related. Laboratory investigations are needed to confirm this apparent increased concentrative ability in the older population. An experimental procedure was developed where subjects are asked to repeat messages presented to one ear (shadowing) while ignoring simultaneous messages in the other ear. High concentrative ability is demonstrated by equivalent shadowing performance with and without simultaneous (and different) messages in the other ear. An experimental study using young (18-29 yrs), middle-aged (40-55 yrs) and old (65-85 yrs) subjects was completed. After controlling for differences in intelligence, hearing loss, and monaural shadowing performance it was determined that age and concentrative ability are inversely related. With increased age there was an increase in dichotic shadowing errors. The decrease in concentrative ability with increased age was also evident when the sample was restricted to those who did not take prescription medication and were not hospitalized within the prior two years and when the sample was restricted to those who made no monaural shadowing errors.

NOTICE OF INTRAMURAL RESEARCH PROJECT

201 AG 00180-03 LPC

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Stress, Coping and Personality in Aging Men and Women

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

Paul T. Costa, Jr., Chief, Personality, Stress and Coping Section, LPC, GRC, NIA

Robert R. McCrae, Research Psychologist, PSC, LPC, GRC, NIA

Alan B. Zonderman, Senior Staff Fellow, PSC, LPC, GRC, NIA

Catherine M. Busch, Staff Fellow, PSC, LPC, GRC, NIA

Theodore M. Dembroski, IPA, PSC, LPC, GRC, NIA

William E. Whitehead, Guest Worker, FSKMC

COOPERATING UNITS (if any)

Laboratory of Cardiovascular Sciences, GRC

Department of Psychiatry, Duke University Medical Center

Epidemiology, Demography, and Biometry Program, NIA

LAB/BRANCH

Laboratory of Personality and Cognition

SECTION

Personality, Stress and Coping

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS

5.4

PROFESSIONAL

4.9

OTHER

0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is concerned with the effects of stressors, coping mechanisms, and enduring personality dispositions on psychological and health outcomes. One study examined mature and ineffective coping efforts associated with the prolonged stress of the nuclear accident at Three Mile Island, replicating earlier findings showing an association between Neuroticism and ineffective coping. Another study examined the association of chronological age with defense mechanism scales; the results revealed only modest correlations with age but suggested a consistent picture of older people as more likely to use defenses related to altruism and socialization instead of confrontation. Three studies done this year on age and personality lend support to previous findings of stability: Six-year stability coefficients for both spouse ratings and self-reports were no different among self-perceived personality change groups; adults ($N > 3,700$) did not differ markedly from college students ($N > 4,200$) on most MMPI content dimensions; and age was found to form only a minor part of the spontaneous self-concept in a study of 245 men and women in the BLSA. Another study identified the interpersonal behavior plane of Love and Status in terms of the five-factor model dimensions of Extraversion and Agreeableness. A series of studies called into question the practice of K-correcting clinical and research scales of the MMPI. Three studies on personality and health replicated in a national sample the finding that Neuroticism is not a risk factor for coronary death; identified antagonistic hostility as a predictor of CHD incidence in the MRFIT study; and, unexpectedly, found greater cardiovascular reactivity to stressors among college-aged females.

ANNUAL REPORT OF THE EPIDEMIOLOGY, DEMOGRAPHY, AND BIOMETRY PROGRAM

NATIONAL INSTITUTE ON AGING

The EDB Program has continued to evaluate its research agenda and priorities in FY88. With the help of the EDB Ad Hoc Scientific Advisory Committee and in consultation with the Director of NIA a number of important decisions have been reached in the past year. In the Fall of 1988 the research staff of the EDB had a 2-day retreat aimed at considering the Program's research directions for the next 5 to 10 years.

We have defined our overarching goals, as understanding the common events and processes of aging, the differentiation of "normal" aging from disease processes, and the identification of potential methods for expanding the period of high quality life. The major endpoints associated with the final goal have to do with: (1) the process of avoiding or delaying the diseases associated with growing older, and (2) effectively compensating for the presence of these conditions when they do occur.

Many of the processes formerly thought to be totally due to aging are at least partially due to disease or environmental factors. For many physiological parameters it has been possible to identify individuals who have little or no decline in function with age. These individuals may be part of the cohort of individuals who we know are now living longer and (presumably) healthier lives. These individuals often are relatively functional into their 80's and 90's. However, successfully growing older usually involves not the absence of disease or physiologic change, but effectively compensating for physiologic changes and diseases. Although it is imperative to continue efforts toward understanding the causes, and preventing the diseases of aging most individuals will suffer from some manifestation or disease associated with growing older. Many will effectively meet that challenge. Those who do can be considered to have aged "well." Detection of the biomedical, behavioral, economic, and social correlates of effective compensation for the diseases and physiologic changes of aging is an area of major emphasis of the EDB program.

As a result of the retreat and our consultation with advisors, the Program has begun to develop priorities for the 1990's. These include: an intent to broaden our research agenda in terms of the number and types of projects while at the same time carefully evaluating the long- and short-term implications of each project on staffing, staff time commitments, and future funding priorities; to focus future efforts on hypothesis-based epidemiologic research; to incorporate biomedical, social and economic aspects into our research designs; to evaluate the potential for cross-cultural and international research in furthering our goals; to promote increased communications within the EDB staff and to broaden participation of the EDB staff in decision making; to use a team approach in project management and analysis to increase Program productivity; to increase the representation of EDB staff in key leadership roles in EDB activities; and to develop a more formal training program in the Epidemiology of Aging, including ongoing internal EDB acquisition and sharing of knowledge through the EDB seminar series.

There has also been a concerted effort to evaluate each ongoing EDB research effort in the light of NIA and EDB programmatic priorities.

1. Established Populations for Epidemiologic Studies in the Elderly (EPESE)

The EPESE studies, to which a major portion of the EDB Program funds were allocated in the first years of the Program, were thoroughly evaluated and major changes in direction have occurred in response to the changing data needs in the field of Aging Epidemiology. Several changes in the management of the EPESE studies were made to improve staff communications and input into planning and implementation. Dr. Joan Cornoni-Huntley, who was the sole Project Officer for all the EPESE contracts left the Program to assume other duties at the Institute. A new, separate Project Officer was named for each of the four EPESE contracts (see Epidemiology Office report). An Assistant Project Officer was designated for each contract as well. An EPESE Working Group consisting of the Project Officers, the Director of EDB, and key EDB scientists and staff was constituted to provide input and advice on decisions needed for project management and to ensure communications and common knowledge regarding all key aspects of the Program. This group met approximately biweekly to review all relevant developments and decisions.

A battery of hypothesis-based physical measurements was added to the 1988 annual contact (third in-home interview) with the participants at the original three locations. Future follow-up plans for those three cohorts have been modified in a request for contract proposals for a new 5-year contract to focus on less expensive secondary data follow-up. No decisions have been made in this regard as to the future directions of the forth center (North Carolina) which has 2 years of funding remaining.

The collaborative publication policies of the EPESE have been modified and streamlined with the intent of facilitating the output of collaborative publications. Consultations are in progress with staff from the National Center for Health Statistics, the University of Michigan Data Archive, and the NIH Associate Director for Disease Prevention, regarding the public release of EPESE data. An initial Professional Services Contract has been requested for computing and data management support; a more extensive long-term arrangement (tentatively approved) will allow the preparation and documentation of data tapes prerequisite to such release. Increased programming demands due to the increased emphasis on publication by staff and programming support needs of the Special Assistant to the Director may conflict with efforts to expedite archiving of the EPESE data, however.

2. Research on Dementia

Research activities relating to dementia form a major part of the EDB research program. Funding ceased for two major projects carried out in the East Boston cohort--the Framingham Dementia Study and the Natural History of Senile Dementia Study. The Demography and Economics Office published an analysis of the national cost of dementia (Huang L, Cartwright WS, Hu T. The economic cost of senile dementia in the United States, 1985. Public Health Reports 1988;103(1):3-7).

3. The National Institute on Aging Macroeconomic-Demographic Model of Health Care and Consumer Expenditures

The National Institute on Aging Macroeconomic-Demographic Model of Health Care and Consumer Expenditures was completed during the last year. Research has also been completed on the optimal coinsurance rate for medigap insurance policies and the demand for various levels of medigap coverage.

4. Other

Analytic activities have continued with data sets from the Last Days of Life study and the NHEFS. While the analysis of NHEFS will continue to occupy staff time, further data collection under EDB aegis is not anticipated for that study.

The Program has increased its productivity in terms of peer reviewed scientific publications during FY88. During the past year the staff has published 29 articles and chapters. In addition 51 have been submitted for publication or are in press. This is a significant increase in scientific output.

EPIDEMIOLOGY OFFICE

Epidemiology Office staff members work with the Associate Director, other EDB Program staff members, other members of the NIA, other investigators at the NIH, Government contractors, the NCHS and other agencies on a variety of analytic, developmental, methodologic, and administrative projects.

Most of the achievements of the Epidemiology Office involved new and continuing analyses of data from established EDB Program projects, including:

1. Established Populations for Epidemiologic Studies of the Elderly (EPESE)

A plan was established defining the content and form of the current and (possibly) future EPESE data-gathering activities. The most essential aspect of this plan involved a shift away from the collection of subjective information for all participants at all sites by annual telephone interview, toward the collection of more objective and hypothesis-related information, including data from clinical and laboratory examination. This decision reflected a general perception that the initial descriptive goals of the EPESE at the three initial sites (East Boston, Massachusetts; New Haven Connecticut; and Iowa and Washington counties, Iowa) will be largely achieved with completion of the seventh contact. Our current plan calls for ongoing surveillance for deaths and hospitalizations. No regularly scheduled contact after completion of the seventh contact (currently being conducted at the three original sites) are called for in the RFP developed for surveillance. Because of the perceived need for clinical and objective data, the protocol for the seventh contact required the development of several new instruments and methods (collection of blood; assessment of physical functioning, vision, etc.). Dr. Guralnik played the central role in this development.

Among the three original EPESE centers, only the New Haven site has an acceptable means for obtaining hospitalization data other than through the possible utilization of data tapes supplied by the Health Care Finance Administration (HCFA). It has not yet been fully demonstrated that adequate, valid, and usable hospitalization information for EPESE participants can be obtained from HCFA, and no documentation recording HCFA's prior agreement to provide such information has been located. On July 12, such an agreement was reached between HCFA staff and EDBP staff. At that meeting it was agreed that HCFA hospitalization data for EPESE participants would be forwarded directly to the EDBP upon request and/or at regular intervals. This arrangement appears highly probable to provide a satisfactory solution to our critical need for hospitalization information. Data available at all sites related to nursing home admissions are currently limited to information collected during the course of routine annual interviews. No alternative method for ongoing ascertainment of this endpoint is yet apparent.

Current plans call for the Duke EPESE project, now conducting its first annual follow-up cycle of interviews (by telephone), to follow the same course of annual contacts as already accomplished at the three original EPESE sites.

A contract is currently being developed (largely by Biometry Office staff) to facilitate the more effective and efficient utilization of the EPESE data already collected. This contract will (1) provide many of the data-management and analysis-supporting services previously provided within the EPESE contracts

with the three original sites, (2) will allow EDBP staff members to be more involved in research rather than technical work, and (3) will greatly facilitate preparation of the data sets for archiving and release. Drs. LaCroix and Guralnik are currently developing a separate new research contract for which one or more of the original EPESE sites may apply (described in a later section). Proposed new research topics to be addressed by this new study include: (1) definition of the most common pathways from disease to disability, (2) determination of rates, risk factors, and course (subsequent morbidity, mortality) for respiratory and urinary tract infections, (3) an examination of co-morbidity patterns, correlates, and consequences (survival, functioning, etc.) to identify common elements in the pathogenesis of age-dependent diseases, and to relate these to the physiologic changes of normal aging. More extensive nursing home data will also be collected under this contract than were collected under the earlier EPESE contracts.

Dr. LaCroix assumed responsibility as Project Officer for the East Boston Senior Health Project EPESE (Brigham & Women's Contract, No. N01-AG-0-2107) and performed a site visit to East Boston in May 1988. Dr. LaCroix prepared the Request for Contracts and OMB clearance package for the ongoing sixth follow-up (in-person interview and examination) of the three original EPESE sites. She also prepared the Requests for Contracts for the long-term renewal of the EPESE focused upon surveillance for mortality and hospitalization events, continued laboratory analysis, and statistical analysis of the baseline and first six years of follow-up.

Dr. Guralnik assumed responsibility as Project Officer for the Iowa 65+ Rural Health Study EPESE (University of Iowa Contract, No. N01-AG-0-2106) and visited that site in May 1988. Project Officer responsibilities for the Yale Health and Aging Project EPESE (Yale University Contract, No. N01-AG-0-2105) and the Piedmont Health Survey of the Elderly EPESE (Duke University Contract, No. N01-AG-4-2110) projects were assigned to Mr. Foley and Mr. Everett, of the Biometry Office. Dr. Guralnik has coordinated the blood collection activities among EPESE sites and the central laboratory in the 1988 in-person assessment which is taking place in East Boston, Iowa and New Haven.

Work began toward preparation of a resource data book for the Duke EPESE corresponding the book previously produced based on the baseline interview data for the three original EPESE sites (Cornoni-Huntley et al. (Eds.): Established Populations for Epidemiologic Studies of the Elderly, Resource Data Book, National Institute on Aging. NIH Publ. No. 86-2443. U.S. Government Printing Office, Washington, D.C., 1986).

Arrangements were made for a special session at the 1988 meeting of the American Public Health Association to be dedicated to: "Longitudinal Community Studies of Older Persons: NIA's Established Populations for Epidemiologic Studies of the Elderly." Dr. White is scheduled to present an analysis of performance on a mental status examination, while Dr. LaCroix (in cooperation with Drs. Guralnik, Curb, and others) will discuss exertional chest pain and risk of fatal and nonfatal coronary heart disease among EPESE participants.

2. NCHS Data Sets and Surveys

Dr. LaCroix and other EDBP staff worked closely with other NIA personnel in developing plans for the Institute's contribution to and utilization of the upcoming third NCHS National Health and Nutrition Examination Survey (NHANES III).

A small professional services contract was awarded to Dr. Jan Kardaun to examine data from the National Hospital Discharge Survey in order to describe rates and types of complications associated with surgical treatment of intervertebral disk disease and with cholecystectomy among persons of differing age and with varying co-morbid conditions (with Dr. White).

Additional follow-up information on vital status and from annual telephone contact was generated as part of continuing follow-up of the NHANES I participants (NHEFS Agreement No. Y01-AG-9-0018; Dr. Cornoni-Huntley).

Dr. Cornoni-Huntley, in conjunction with Drs. Jacob Feldman and Robert Huntley continued their efforts as editors of a forthcoming book to be entitled: "Health Status and Well-Being of the Elderly." That monograph, now nearing completion, will describe the NHANES I/NHEFS and will present information on selected aspects of the health of those participants who were 55 and older at the baseline examination.

3. Developmental activities involving other Institutes

Dr. Curb continued to consult with NHLBI staff in their initiation of a multi-center project on risk factors for heart disease in the elderly.

During this year there was further development of opportunities for defined, cooperative analyses of data from the Systolic Hypertension in the Elderly Project (SHEP). Although the NIA has been a major contributor of funds for SHEP, the NHLBI has taken the major role in management and has received the lion's share of recognition. Drs. Page and Sluss-Radebaugh (NIA extramural scientists) have represented the NIA in recent years and have recognized the potential of the SHEP data for many aspects of research on aging. NIA's access to these data is now further facilitated by Dr. Curb's prior position of leadership as a SHEP principal investigator and his continuing participation as Vice Chair of the Publications and Presentation Committee of the SHEP Cooperative Research Group. Dr. Curb is also a participating member of the SHEP Steering Committee. Further development of this opportunity for defined, cooperative analyses is anticipated.

As part of the planning for the 1988 EPESE examination, several contacts with other Institutes were made by Drs. Guralnik, Curb, Cornoni-Huntley, and White for the purpose of soliciting advice and collaborative funding of specific study components. Despite expressions of serious interest from several, none of the Institutes followed through with a commitment of financial support.

4. Development of research projects in the Pacific and Asia.

Further progress was made toward the possible establishment of a field station in Hawaii to coordinate EDBP research projects on aging and dementia in Hawaii and the Asia/Pacific region (China, Japan).

Specific developmental activities included:

- a tentative agreement reached with the NHLBI to collaborate in a re-examination of the 6000 living participants in the Honolulu Heart Study (HHS).
- NIA cooperation with the Administration on Aging to support an effort by the State of Hawaii to (a) inventory the professional resources available in Hawaii to assist with epidemiologic studies of aging and Dementia and to assess the ability and willingness of the relevant institutions and individuals to cooperate in such a study, (b) to prepare a summary of available demographic information related to the state's older citizens, and (c) to host a preliminary workshop dealing with the development of methods needed for the proposed study.
- a panel of expert advisors identified for the proposed HHS study, including: Dr. Eric Larson (expertise in methods and instruments for diagnosis of the major types of dementia; has interest in the study of dementia among persons of Japanese ancestry, and has access to Seattle's Japanese population), Dr. Evelyn Teng (neuropsychologist with special expertise in screening and neuropsychological evaluation in dementia; experienced and interested in such studies in Japanese and Chinese populations), and Dr. Paul Sherr (expertise in population studies and registries of dementia and aging). While these three persons represent the core panel, several others have indicated willingness to provide occasional consultations and advice, including: Dr. Robert Katzman, Dr. Jacob Brody, and Dr. Denis Evans. The workshop mentioned above (tentatively planned for late summer or early fall, 1988) will be attended by the three core members of the advisory panel, Dr. White and Dr. Curb, and (if possible) representatives from the Tokyo Metropolitan Institute of Gerontology and the Radiation Effects Research Foundation.
- discussions with Dr. L. Kurland (Mayo Clinic) concerning the possible involvement of the proposed field station in ongoing studies of dementia and allied neurological diseases among the Chamorro people of Guam.
- discussions with Dr. Eric Larson (Seattle ADRC) concerning possible development of a Seattle-Tokyo cooperation to facilitate the development of a study of dementia at the Tokyo Metropolitan Institute of Gerontology, designed to yield information comparable to that generated by the Hawaii study; the three-way cooperation to be organized and managed through the proposed field station.
- plans to establish an EDBP investigation of aging and dementia in China using methodologies corresponding to those to be used in Hawaii and Tokyo; to be coordinated through the proposed field station (see below). Drs. Curb and White traveled to Wuhan and Beijing, China, to investigate the feasibility of such an investigation. A professional services contract was established

with the University of Michigan to examine and report to us the results of a pilot study of aging conducted during April by the Population Institute of Wuhan University.

- plans for cooperating in epidemiologic studies of aging and dementia in Japan using methodologies corresponding to those already utilized in other previous or planned EDBP studies (EPSE, Natural History of Senile Dementia Study, Framingham Dementia Study, Honolulu Dementia Study, CLESA - the proposed EDBP clinical laboratory for epidemiologic studies on aging). The EDBP was visited by Dr. Shibata of the Tokyo Metropolitan Institute of Gerontology (TMIG), and Dr. Curb visited the TMIG to conduct further planning toward such cooperation.

5. Other International Activities

Drs. Cornoni-Huntly and Guralnik organized and participated in a meeting in Italy in November 1987. EDBP participation in this activity, originally requested by Dr. Williams, is not envisioned as leading to any intramural research project; rather, it was undertaken to assist Italian investigators in establishing their epidemiologic research on aging and dementia in Italy, and to facilitate the exchange of information between the East Boston Neighborhood Health Center (Brigham & Women's contract) and these same Italian researchers. Additional meetings to further develop plans for the Boston-Italy collaboration, held in Boston in May 1988, were attended by Dr. Cornoni-Huntley.

EDBP staff participated in a joint Israel-NIA meeting on epidemiologic aspects of aging, focused on the development of plans for future cooperative and comparative research. (Drs. White, Curb, Cornoni-Huntley and Guralnik)

EDBP staff participated in meetings of the WHO Special Program for Research on Aging (SPRA) to develop recommendations regarding international research. Dr. Curb represented the NIH in the consultation group on Healthy Aging, while Dr. White participated in the meeting of the Dementia Research consultation group.

6. Natural History of Senile Dementia

This study, conducted at East Boston (Contract No. N01-AG-1-2106) was completed during fiscal year 1988. In July the contractor supplied the EDBP with a final data tape and documentation. While several key analyses of these data by the contractor are already underway, it is expected that supplementary analyses by EDBP staff will be forthcoming. The contractor has recently submitted two manuscripts for publication, and will present a report on survival patterns of demented study participants at the 1988 meeting of the American Public Health Association.

7. Studies of Dementia in Framingham

Contract support for the Framingham Dementia Study (Agreement No. Y02-AG-2-0040) ended. NIA funding, through an interagency agreement with the NHLBI, allowed for the inclusion of the Folstein Mini-Mental State Examination (MMSE) in cycles 17, 18, and 19, and for the clinical evaluation and diagnostic classification of persons suspected of being demented on the basis of poor performance on the MMSE. Analyses are underway seeking associations between

cognitive impairment and dementia (categorized as to most likely type) and potential risk factors. The initial focus of these analyses involved possible associations between impaired cognitive functioning and (a) educational attainment (found to be strongly predictive of performance but with little influence on the deterioration of cognitive performance with advancing age), and (b) elevated blood pressure (also found to have only a modest independent association with cognitive performance; see below). Other analyses are underway to examine relationships between performance on a battery of neuropsychological tests and results of an audiometric examination. Analyses are planned to examine relationships of cognitive functioning and dementia with (a) diabetes, and (b) vision and eye disease (macular degeneration and cataract). Other analyses currently underway will examine the course and prognosis associated with poor performance on neuropsychological tests of cognitive functioning, and estimates of the lifetime incidence (identical with prevalence at death) of dementia. The contractor is involved in analyses of the prognostic and diagnostic meaning of patterns of performance on the several neuropsychological tests administered, and on an estimate of the age-specific incidence of dementia.

8. Analytic and developmental accomplishments by Epidemiology Office Staff

Dr. LaCroix co-authored seven research papers which have been submitted to peer-reviewed journals for publication. Her co-authors include investigators at the Johns Hopkins University, Columbia University, Dalhousie University (Nova Scotia, Canada), the Honolulu Heart Program, NIA, and the National Center for Health Statistics. The topics of these papers include studies of risk factors for coronary heart disease (physical activity, left ventricular hypertrophy, occupational strain) and hypertension.

Dr. LaCroix has submitted two research papers to peer-reviewed journals for publication. The first is a study of the prevalence and cardiovascular risk correlates of Rose Questionnaire angina in black, white, and Mexican-American women and men, focusing on differences in younger and older subjects. The second is a prospective investigation of risk factors for pneumonia in the NHEFS including chronic conditions, nutritional status indicators, and pulmonary function.

Dr. LaCroix is currently completing a collaborative investigation with the EPESE data examining the relationship of exertional chest pain to risk of coronary heart disease mortality during 3 years of follow-up.

Dr. LaCroix has initiated a study of dehydroepiandrosterone in relation to the development of coronary heart disease in the Honolulu Heart Study cohort working with Drs. Yano and Reed in Honolulu. NIA will fund the laboratory analysis of frozen serum for DHEA determinations.

Dr. Guralnik has been author or co-author on a number of scientific papers on which he has collaborated with outside researchers. These researchers have been from Yale University, The California Department of Health Services, Boston University, The University of California at San Francisco, The National Center for Health Statistics and the University of Southern California.

Dr. Guralnik is currently completing a collaborative investigation with NIA and EPESE researchers which examines the changes in disability in the years prior to death.

Dr. Guralnik is pursuing research using the National Center for Health Statistics' Supplement on Aging to investigate the occurrence of multiple morbidity and the impact of multiple morbidity on disability. This research is a collaborative effort between NIA and NCHS researchers.

Dr. Guralnik is collaborating with Dr. Edward Schneider on research which examines future health care costs and their relationship to the future growth of the older population.

Dr. Guralnik has provided consultation to a number of research projects in aging in the area of physical functioning and disability and the assessment of objective measures of physical performance. He has consulted with Dr. Rena Pasick of the San Francisco Community and Home Injury Prevention Project for Seniors; Dr. Stephanie Maggi of the University of Padua, Italy; Dr. Vicki Zunzunegui, Escuela Andaluza de Salud Publica, Granada, Spain.

Ms. Dorly Deeg, a guest researcher from the Netherlands working with Dr. White and other EDBP staff, submitted five manuscripts for publication (two accepted, three pending) and three abstracts for presentation at national and international meetings. These involved the development of methods for the assessment of factors influencing survival time, the identification of factors influencing survival (with White and Curb), interactions between and among factors associated with shortened survival time (with White and Williams), and the association of body wieight change and survival for specific causes of death (with Miles). Ms. Deeg returned to The Netherlands in the spring, then visited the EDBP in July to present the results of her most recent analyses to EDBP staff and to complete discussions with Dr. White prior to completion of a project describing the factors predicting survival among participants in the NHEFS.

Dr. Toni Miles completed a 2-year assignment with EDBP as a National Research Service Awardee and accepted a faculty position at the University of Illinois School of Public Health. During the year she completed two analyses of in-hospital deaths and cardiopulmonary resuscitation (both submitted, one accepted, one pending), and was involved as the senior author or a co-author of several studies presented at national meetings involving anthropometric issues, methodological issues related to revisions of the standard death certificate, and black-white differences in late life morbidity and mortality.

Dr. Ingrid Liu, finishing the second year of her epidemiology traineeship (her first year of preceptorship with EDBP), completed one analysis of factors associated and with macular degeneration (with Dr. White) and a second analysis examining associations between macular degeneration and lens-opacifying disease (expressed as lens opacities, cataract, and aphakia; with Drs. White and LaCroix). In a separate analysis of data from the Baltimore Epidemiologic Catchment Area Study, Dr. Liu (with Dr. J. Anthony, of the Johns Hopkins University) confirmed the utility of a single mental status test score for predicting subsequent development of mental impairment sufficiently severe as to preclude the participant's completion of a personal interview.

Dr. Danyang Chen joined the EDBP in April as a Visiting (Fogarty) Fellow. Dr. Chen, a physician with training in neurology and epidemiology, worked with Dr. White to complete the initial phases of an analysis of relationships between performance on tests of cognitive functioning and pure-tone audiometric test results in Framingham Heart Study Participants. Initial results suggest that most of the adverse effect of diminished hearing acuity among older participants can be attributed to the co-association with advanced age, and that mild or moderate hearing impairment by itself has only a modest association with poor neuropsychological test performance. Dr. White and Ms. Losonczy (Biometry Office) submitted a manuscript for publication summarizing incident cerebrovascular disease among participants in the NHEFS. A second phase of the analysis, utilizing a modified endpoint definition and focused on nutritional and anthropometric predictors of stroke, is being prepared for submission (White, Losonczy, and Curb). A related analysis of these same data, carried out by Dr. Steve Kittner (Department of Neurology, University of Maryland School of Medicine), Dr. White, and Ms. Losonczy, suggests that most of the increased risk for stroke among black participants can be attributed to hypertension. Drs. White and William McWhortor (an Epidemiology Trainee with the NCI) completed an analysis of clinically recognized dementia among participants in the NHEFS; a manuscript has been forwarded for Institute clearance. Dr. White was a co-author of eleven other manuscripts (four accepted or in press, seven submitted or in review).

Several members of the Epidemiology Office worked with Dr. Curb in the preparation of a manuscript on "Effective Aging." In addition to producing the manuscript, this effort resulted in a very useful focusing of conceptual issues, and is likely to have a lasting effect on the Program's future research goals.

In September 1987 plans were made to begin a regular EDB Program Seminar Series. The series coordinated by Dr. LaCroix with the assistance of Drs. White, Guralnik, and Curb was designed to bring experts in to discuss specialties of interest to the EDB Program researchers to help plan future studies and enhance our knowledge base in content areas that are relatively new or persistently challenging. A regular seminar day and time was selected (Friday afternoon at 2 p.m.), a mailing list was developed as well as a plan to pursue speakers who may be visiting Bethesda. The series has been well received by other NIA staff members and has also been attended by scientists from the Johns Hopkins University, NCHS, the NHLBI, and other Institutes.

Fall Program of the EDBP SEMINAR SERIES:

David Herrington, M.D., was our first lecturer and his topic was "DHEA and Coronary Artery Disease: Relevance to progression of age-related disease processes."

Carl F. Pieper, a biostatistician from Columbia University School of Public Health, was our second lecturer and his topic was "experience with and approaches to the analysis of repeated measures of blood pressure."

Larry J. Brant, Ph.D., Statistician, Longitudinal Studies Branch, BLSA, GRC, "Quantitative examples in longitudinal data analysis and repeated measures designs."

Linda Fried, M.D., M.P.H., Director of the Geriatric Assessment Center at The Johns Hopkins University Hospital discussed a multidisciplinary approach to geriatric assessment.

Emanuel Thorne, an economist from Yale University and a independent consultant in Washington, DC discussed "fetal tissue transplants in the treatment of neurological disorder."

Rubin Andres, M.D., Chief, Laboratory of Clinical Physiology, GRC, discussed "Body weight and mortality: Should we strive to be thin in old age?"

Lon R. White and Dmitry Goldgaber, NINCDS discussed current developments in Alzheimer disease.

Winter Program

Steven Cummings, M.D., Assistant Professor of Medicine and Epidemiology, School of Medicine, University of California at San Francisco, discussed studies of falls and osteoporotic fractures.

Lisa Berkman, Ph.D., Assistant Professor of Epidemiology, Department of Epidemiology, Yale University School of Medicine, discussed recent findings from the Recovery from Illness Study.

Spring Program

Charles H. Hennekens, M.D., Dr.P.H., Harvard Medical School, Brigham and Women's Hospital, discussed a randomized controlled trial of aspirin and risk of cardiovascular disease in healthy physicians.

Hiroshi Shibata, M.D., Tokyo Metropolitan Institute of Gerontology, discussed longitudinal changes in markers of aging and predictors of death between ages 70 and 80: The Koganei Study.

Robert B. Wallace, M.D., The University of Iowa, discussed patterns and health implications of medication use in older people: The Iowa 65+ Rural Health Study.

Summer Program

William Adler, M.D., Chief, Clinical Immunology Section, Laboratory of Clinical Physiology, GRC, discussed markers of immune function in older people: Applications in epidemiologic studies.

Juha Pekkanen, M.D., Department of Epidemiology, National Public Health Institute, Helsinki, discussed a longitudinal study of cardio-vascular disease with repeated measures in an older cohort in Finland.

Gary Andrews, M.D., Chairman, Primary Care and Community Medicine, School of Medicine, The Flinders University of South Australia, will discuss needs of the elderly in developing countries of the Western Pacific Region.

We look forward to our Fall Program, for which we have already lined up three exciting seminars - Dr. J. Michael McGinnis, Deputy Assistant Secretary for Health, will give us his impressions or ideas in the areas of disease prevention and health promotion in older individuals; Dr. Barbara Klein, Associate Professor, Department of Ophthalmology, University of Wisconsin-Madison, will discuss vision impairment and eye disease; and Dr. Liu Yan, of the Chinese National Ministry of Health, will discuss aging in China.

Research Highlights for FY88

An analysis of NHEFS data showed that among subjects who died during the follow-up period, pneumonia was equally likely to be a cause of death among younger (aged 55 to 64 at baseline) subjects as among older subjects (aged 65 to 77 at baseline). In this same study, body mass index and arm muscle area were found to be inversely related to risk of pneumonia among men, and serum albumin was found to be inversely related to risk of pneumonia among women, after controlling for all chronic condition risk factors (LaCroix, Lipson, White).

An analysis of EPESE data showed that among subjects without previous history of heart attack, those with exertional chest pain were at increased risk of coronary heart disease mortality during the following 3 years. Exertional chest pain was a stronger risk factor for older women than for older men. Other qualifiers of exertional chest pain such as the need to rest or take medication, whether the pain is subsequently relieved, time until relief, and the location of the pain, did not increase the sensitivity of the angina classification in terms of predicting future risk of CHD mortality associated with exertional chest pain (LaCroix and others).

An analysis of NHANES I data showed that left ventricular mass index as measured by electrocardiogram was primarily associated with level of systolic blood pressure, and was not independently associated with age (LaCroix and others).

An analysis of post-menopausal women who had undergone arteriography at the Johns Hopkins Hospital showed that participation in a regular exercise program was inversely associated with atherosclerosis (≥ 50 percent vs. < 25 percent maximal stenosis), independent of standard coronary risk factors. A higher level of leisure-time physical activity was also inversely associated with atherosclerosis, particularly among older women and nonsmokers (LaCroix and others).

In analyses of the Census Bureau's past projections of the population age 65 and older, it was found that consistently low projections of this population were made as a result of underprojecting the rapid mortality declines which have occurred in the older population. Published projections for the next

century may also underestimate the population 65 and older and alternative projections should be considered, especially for the rapidly growing population aged 85 and older (Guralnik, Yanagashita and Schneider).

In a nationally representative sample of adults aged 55 to 75, 2.2 percent were found to develop a pressure sore during approximately 10 years of follow-up. Increased risk of future pressure sore development was found for smokers, those reporting being relatively inactive, having poor self-assessed health status, having dry or scaling skin on physician's exam, having a neurologic abnormality on exam and being anemic (Guralnik and others).

Long-term predictors of high levels of physical functioning were examined in a representative sample of persons born between 1895 and 1919 and followed from 1965 through 1984. After adjustment for age and functional status at baseline, the following variables were predictive of high functioning at follow-up 19 years later: race (nonblack), higher family income level, absence of hypertension, absence of arthritis, absence of back pain, being a nonsmoker, having normal weight and consuming moderate amounts of alcohol. Neither sex was more likely to have high function at follow-up. This was demonstrated to be the result of the counterbalancing effects of higher survival in females but greater likelihood of high functioning among surviving males.

Following a preliminary examination of "conventional" risk factors previously shown to predict the occurrence of strokes (see last year's source book), Dr. White, Ms. Losonczy, and Dr. Curb undertook an in-depth investigation of nutritional and anthropometric predictors. This analysis fails to support a previously reported association between high dietary potassium intake and reduced incidence of stroke. Associations of stroke with skinfold thickness and with sitting height do not appear to be statistically significant in this study. Among women, lower dietary intake of fruits and vegetables appears to be associated with an increased risk for stroke, while use of supplementary vitamins is weakly associated with an increased risk in both sexes.

Although macular degeneration (of the retina) and opacifying disease of the lens are both strongly related to advancing age, their pathogeneses are generally thought to be unrelated. Among NHANES I participants, Dr. Liu demonstrated an especially interesting relationship: the odds that an individual would have concomitant macular degeneration were significantly increased among persons with lens opacities (small lesions, rather than mature cataracts), slightly increased (not statistically significant) among those with cataracts, and much greater among aphakic persons (almost always attributable to prior cataract extraction). These observations suggest a sharing of some pathogenic factors (accelerated aging? exposure or vulnerability to photooxidative damage?), and support a previously suggested protection of the retina by the cataractous lens and an increased vulnerability of the retina to the injurious effects of light once the lens has been removed (Liu, White, and LaCroix).

A second analysis conducted by Dr. Liu confirmed an association of macular degeneration with hypertension, but not (in contrast to other reports) with nutritional intake of vitamin A or other anti-oxidants (Liu and White).

An analysis conducted by Deeg, White, Williams and Curb illuminated a problem of both methodologic and conceptual importance. While conventional

multivariate analyses generally assume an independence of the influences of independent variables (as risk factors) upon the dependent variable (as illness or death), the clinician "knows" that the quality and quantity of an individual's burden of ill-health characteristics will modify subsequent patterns of illness and survival. Using data from the Dutch longitudinal study, this analysis confirmed that survival was influenced by the nature of the combinations of illnesses and risk factors, but demonstrated no constant pattern of interaction (beyond a linear additive effect) with an increasing burden of risk factors or ill-health indicators. While these analyses fail to support the intuitive notion that a damaging factor will always be more harmful to the person with other risk factors or with multiple ill-health conditions, they nonetheless confirm a complexity among multiple independent and dependent health variables greater than that generally assumed with the usual multivariate models used to predict mortality.

CONTRACT

Name and Number : DUKE UNIVERSITY MEDICAL CENTER (NO1-AG-4-2110)

Title : Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: September 30, 1984

Current Annual Level : \$880,000

Objectives : Duke University Medical Center is studying an elderly population of at least 4,500 noninstitutionalized persons, 65 years of age or older, and of which at least 50 percent is black and approximately 30 percent to 40 percent is white. The population is stable with a wide range of socioeconomic status in both black and white groups. The influence of social, environmental, behavioral, and economic forces on the mortality, morbidity, and utilization of health services in the study population will be investigated.

Methods Employed : Descriptive and analytical epidemiologic studies of existing problems and surveillance of newly developing problems all with an emphasis upon future intervention and prevention will be conducted. Investigators will conduct cross-sectional and prospective studies as well as more detailed problem-related studies in a carefully defined and accessible population using standard field and analytical techniques. During the first year the population was defined ecologically in terms of social, political, and demographic characteristics; and working relationships were established with the public and professional groups within this population.

Major Findings : Instruments were developed and pretested, specific research goals were defined, and coordination with the three existing population studies developed.

Significance to Biomedical Research: The NIA began funding three population studies of the elderly to determine the influences of social, environmental, behavioral, and economic forces on the mortality, morbidity, and utilization of health services in the elderly. These studies, however, were not fully representative of the U.S. elderly, specifically, they did not include a significant proportion of blacks. It is well known that distributions of certain risk factors and diseases differ between U.S. blacks and other racial groups. Therefore, the purpose of this contract is to conduct epidemiologic investigations in an elderly population of which at least 50 percent is black in order to develop new knowledge concerning the medical and social factors in health and diseases of the aging black population.

Proposed Course : From January 1986 to June 1987, 4,165 baseline interviews were conducted in Durham, Franklin, Granville, Vance, and Warren Counties in North Carolina. From January 1987 to June 1988, the first annual telephone follow-up was conducted and the second follow-up of 4,095 respondents was conducted from January 1988 to May 1988. The second in-person follow-up will be conducted from January 1989 through June 1990.

CONTRACT

Name and Number : UNIVERSITY OF IOWA (NO1-AG-0-2106)

Title : Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: June 30, 1980

Current Annual Level : \$849,437

Objectives : The purpose of this project is to conduct epidemiologic investigations in a community to develop new knowledge concerning the medical and social factors in health and diseases of the aged. Within the major prospective study are substud problems of pain, vision, hearing, sleep, drug use, constipation, social support and other pertinent areas.

Methods Employed : The project shall include cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population will be included.

Major Findings : The number of leisure activities spouses shared was a positive predictor of satisfaction during retirement for both husbands and wives, which supports an extension of the activity theory of aging to satisfaction in retired couples. Social network interaction with friends was a positive predictor of satisfaction in retirement for husbands only, providing differential support by gender for the activity theory of aging.

Significance to Biomedical Research: The population over age 65 has been steadily increasing both in relative and absolute numbers. With this increase has come an awareness of a variety of health and social problems which are creating problems for our social and physical environment. To provide new knowledge, it is important to have studies representing existing conditions in a community population. Within obvious logistical constraints populations will be available to the NIA scientific community for specific studies.

Proposed Course : Continued surveillance during a 5-year period (1989-93) for two major endpoints of the EPESE: mortality and hospitalization. The additional data will be integrated with the previous data collected and the techniques shall be compatible with the techniques used in the previous EPESE (involving no or minimal direct contact with study subjects) will be used to ascertain the occurrence of hospitalization events including the time of these events, the admitting and discharge diagnosis, and the subjects' discharge dispositions. Surveillance systems will also be used to monitor deaths among study participants including the time of these deaths, procurement of death certificates, and nosologist coding of causes of death.

Publications : Dorfman, LT, Heckert, DA, Hill, EA, Kohout, FJ. Retirement satisfaction in rural husbands and wives, Rural Sociology 1988; 53(1):25-39.

CONTRACT

Name and Number : PETER BENT BRIGHAM HOSPITAL (NO1-AG-0-2107)

Title : Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: June 30, 1980

Current Annual Level : \$1,221,238

Objectives : The purpose of this project is to conduct epidemiologic investigations in a community to develop new knowledge concerning the medical and social factors in health and diseases of the aged. Within the major prospective study are substudies on problems of pain, vision, hearing, sleep, drug use, constipation, social support and other pertinent areas.

Methods Employed : The project shall include cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population will be included.

Significance to Biomedical Research: The population over age 65 has been steadily increasing both in relative and absolute numbers. With this increase has come an awareness of a variety of health and social problems which are creating problems for our social and physical environment. To provide new knowledge it is important to have studies representing existing conditions in a community population. Within obvious logistical constraints populations will be available to the NIA scientific community for specific studies. High priority short term studies will be encouraged.

Proposed Course : Continued surveillance during a 5-year period (1989-93) for two major endpoints of the EPESE: mortality and hospitalization. The additional data will be integrated with the previous data collected and the techniques shall be compatible with the techniques used in the previous EPESE contracts. During the 5-year period of the contract surveillance systems (involving no or minimal direct contact with study subjects) will be used to ascertain the occurrence of hospitalization events including the time of these events, the admitting and discharge diagnosis, and the subjects' discharge dispositions. Surveillance systems will also be used to monitor deaths among study participants including the time of these deaths, procurement of death certificates, and nosologist coding of causes of death.

CONTRACT

Name and Number : YALE UNIVERSITY (NO1-AG-0-2105)

Title : Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initialed: June 30, 1980

Current Annual Level : \$675,000

Objectives : The purpose of this project is to conduct epidemiologic investigations in a community to develop new knowledge concerning the medical and social factors in health and diseases of the aged. Within the major prospective study are substudies on problems of pain, vision, hearing, sleep, drug use, constipation, social support and other pertinent areas.

Methods Employed : The project shall include cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population will be included.

Significance to Biomedical Research: The population over age 65 has been steadily increasing both in relative and absolute numbers. With this increase has come an awareness of a variety of health and social problems which are creating problems for our social and physical environment. To provide new knowledge it is important to have studies representing existing conditions in a community population. Within obvious logistical constraints populations will be available to the NIA scientific community for specific studies.

Proposed Course : Continued surveillance during a 5-year period (1989-93) for two major endpoints of the EPESE: mortality and hospitalization. The additional data will be integrated with the previous data collected and the techniques shall be compatible with the techniques used in the previous EPESE contracts. During the 5-year period of the contract surveillance systems (involving no or minimal direct contact with study subjects) will be used to ascertain the occurrence of hospitalization events including the time of these events, the admitting and discharge diagnosis, and the subjects' discharge dispositions. Surveillance systems will also be used to monitor deaths among study participants including the time of these deaths, procurement of death certificates, and nosologist coding of causes of death.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 02010 10 EDBP

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

NHANES I EPIDEMIOLOGIC FOLLOWUP STUDY (NHEFS)

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Joan Cornoni-Huntley, Ph.D., M.P.H.

COOPERATING UNITS (if any)

National Center for Health Statistics, Division of Analysis; NCI; NHLBI; NIADDK; NIMH; NIAAA; and NINCDS.

LAB/BRANCH

Epidemiology Office

SECTION

Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of this project is to design and complete a follow-up of persons examined in the NHANES I to study how factors previously measured relate to the health conditions that have developed since the survey. The three major areas for prediction of outcome are 1) risk factors for chronic disease; 2) nutrition; and 3) health care utilization. The survey has a household interview including self-reporting of health conditions, dietary history and behavioral and social status plus some physical measurements such as blood pressure, height, and weight. Death certificates and hospitalization records will be acquired for all reported events. Additional follow-up information on vital status and from annual telephone contact was generated as part of continuing follow-up of the NHEFS. Further data collection under EDBP aegis is not anticipated for this study. Analysis will continue to occupy EDBP staff time.

Leaverton PE, Sorlie PD, Kleinman JC, Dannenberg AL, Ingster-Moore L, Kannel WB, Cornoni-Huntley JC. Representativeness of the Framingham risk model for coronary heart disease mortality: A comparison with a national cohort study. J Chron Dis 1987;40(8):775-784.

Rautaharju PM, LaCroix AZ, Savage DD, Haynes SG, Madans JH, Wolf HK, Hadden W, Keller J, Cornoni-Huntley J. Electrocardiographic estimate of left ventricular mass vs. radiographic cardiac size and the risk of cardiovascular disease mortality in white and black men and women: Results from the NHANES I Epidemiologic Follow-up Study. Am J Cardiology 1988;62:59-66.

Guralnik JM, Harris TB, White LR, Cornoni-Huntley, JC. Occurrence and predictors of pressure sores in the National Health and Nutrition Examination Survey Followup. J Amer Geriatrics Society, 1988(in press).

CONTRACT

Name and Number : PETER BENT BRIGHAM HOSPITAL/
EAST BOSTON NEIGHBORHOOD HEALTH CENTER
(NO1-AG-1-2106)

Title : Senile Dementia: Natural History in a
Noninstitutionalized Population

Date Contract Initiated: June 16, 1981

Total Cost of Contract : \$2,202,359

Objectives : The objective of this study is to describe the course of general health and cognitive decline in a group of SDAT victims and controls.

Methods Employed : Persons suspected of being demented because of performance on a screening examination will receive a neurological and neuropsychological evaluation. SDAT cases and a number of matched controls will then be reexamined at yearly intervals over a period of approximately 3 years; thereafter the cases and controls will be followed as defined by their participation in another EDBP study (EPESE)--for death, hospitalization, and institutionalization end points.

Major Findings : The results of this study, now in preparation, are remarkable for a substantially higher than expected prevalence of dementia, with a high proportion of the cases of dementia being attributed to Alzheimer's disease. All of the cases were living in the community at the time the dementing illness was found, and the dementia had been recognized as such by the family and health care professionals only rarely.

Significance to Biomedical Research/Justification: This study will provide a better understanding of the prognosis and clinical course of SDAT.

Proposed Course : The contract expired June 30, 1988.

Publications : Scherr, PA, Funkenstein, H, Albert, MS, Cook, NR, Ronser, B, Hennekens, CH, Chown, M, White, L, Taylor, J, and Evans, DA. Correlates of cognitive function in an elderly population, Am J Epidemiol 1988; (in press).

NOTICE OF INTRAMURAL RESEARCH PROJECT

PHYSICAL AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

Z01 AG 04003 07 EDBP

PERIOD COVERED

October 1, 1987, to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Dementing Illness in the Framingham Heart Study

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Lon R. White, M.D., M.P.H.
Chief, Epidemiology Office, EDBP, NIA
Jack M. Guralnik, M.D., Ph.D.
Senior Staff Fellow, Epidemiology Office, EDBP, NIA
Andrea Z. LaCroix, Ph.D.
Epidemiologist, Epidemiology Office, EDBP, NIA

COOPERATING UNITS (if any)

NHLBI

LAB/BRANCH

Epidemiology Office

SECTION

Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS.

0.5

PROFESSIONAL:

0.5

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Demented subjects are identified by a 2-phase evaluation: administration of the screening test as part of the regular biennial examination, coupled with neurological and neuropsychological evaluations of participants who fail the screening test. A second group of dementia cases will be identified from among recently deceased study participants based on: (a) poor performance on neuropsychological tests administered approximately 5 years ago, (b) review of medical records, and (c) telephone interviews with a surviving family member.

Continuation of this project has as its major goals: (1) longitudinal observation of persons previously identified as demented, [a] to confirm the diagnosis, and [b] to develop a better understanding of common patterns of progression; and (2) identifying new dementia cases, [a] to increase the power of other studies, and [b] to define incidence rates more accurately.

Publications:

Farmer ME, White LR, Abbott RD, Kittner SJ, Kaplan E, Wolz MM, Brody JA, Wolf PA. Blood pressure and cognitive performance: The Framingham Study, Am J Epidemiol 1987;126(6):1103-14.

DEMOGRAPHY AND ECONOMICS OFFICE

During FY88 a paper was published entitled, "The Economic Cost of Senile Dementia in the United States, 1985." The authors are Drs. Lien-fu Huang, William S. Cartwright, and Teh-wei Hu. Combining direct and indirect costs, the total cost of Alzheimer's disease and other related dementias is estimated to be \$88 billion. The direct total cost is \$13.26 billion which includes \$6.36 billion of medical care costs, \$2.56 billion of nursing home care costs, and \$4.34 billion of social agency service costs. The total indirect cost is \$74.63 billion which includes \$31.46 for community home care and \$43.17 billion for loss of human capital.

A paper presented at the XIIIth Congress of the International Association of Gerontology was published. The paper was titled, "The National Institute on Aging's Health Care Expenditures Model," and was authored by Drs. Joseph M. Anderson and William S. Cartwright. It describes the underlying theory of the Macroeconomic-Demographic Model (MDM), and the basic steps involved in the development of the model. An appendix provides tables on average health care expenditures by type of service and by source of payment of various demographic groups from the 1980 National Medical Care Utilization and Expenditures Survey.

A research paper entitled, "Demand for Health Insurance by the Elderly: A Micro-simulation Model," has been submitted for review. This paper developed a micro-simulation model to explain and estimate the optimum Medigap insurance coverage for the elderly with different levels of insurance premium subsidy. Data from the 1977 National Medical Care Expenditure Survey (NMCES) are used; and the theory of expected utility maximization is applied.

In an extension of the above work, a new paper is being prepared entitled, "The Demand for Medigap Insurance, Adverse Selection, Moral Hazard, and Market Equilibrium." This examines the market implications of having heterogeneous individuals demand medigap policies in a competitive market. The simulation model projects the number of purchases, the average premium, the average risk aversion, elasticity of demand, and average expenditure function.

A research paper entitled, "Demand for Supplemental Health Insurance and its Effects on Health Care Expenditures among the Elderly," was prepared by Drs. Teh-wei Hu, Lien-fu Huang, and William S. Cartwright for presentation at the Health Economics Research Organization Session, Allied Social Sciences Annual Meeting, December 28-30, 1987. This paper explores a number of empirical models of the demand for Medigap policies and the utilization of medical care. Important independent variables are employment, age, sex, race, education, health status, and income. Further research was suggested to extend the model in the area of insurance premium determination. A new paper is being written to focus on the multinomial logit approach to modeling the determinants of the choice of the elderly to be in a high, medium, or low coverage Medigap plan, and also the impact of these various degrees of ownership in the utilization of medical service by the elderly. Preliminary results indicate the importance of socioeconomic and health status on the amount of coverage. Nonwhites are at a particular disadvantage in the outcome of the private markets for Medigap policies. This disadvantage carries over into the utilization of medical services.

A research paper entitled, "Health and Retirement: A Followup Study" is being revised by Drs. Cartwright and Cornoni-Huntley. This paper estimates the impact of heart disease, arthritis, and respiratory disease on the work outcomes of cohort of males who were initially working at the time of the NHANES I study and who were alive and interviewed in the NHANES Epidemiologic Follow-up Study (NHEFS). The presence of self-assessed arthritis and respiratory diseases were significantly and negatively associated with participation in the labor market. Additional work is being done on separate regressions for those reporting a disease.

ICF, Incorporated completed a contract (AG-2-2138) entitled, "Health Expenditures and the Aging Population: Computer Modeling," and the contract (AG-3-2117) entitled, "A Study on Aging, Health and Consumer Expenditures." The results are being prepared for publication in the monograph entitled, "The Macroeconomic-Demographic Model of Health Care and Consumer Expenditures." Publication clearance was received from the Office of the Assistant Secretary for Public Affairs, DHHS. A second publication from these contracts has also been approved which is entitled, "Future Health Care Expenditures and Consumer Expenditures Under Alternative Scenarios." The Interagency Agreement with the Office of the Assistant Secretary for Planning and Evaluation has also been completed.

"Updating and Revising the Macroeconomic-Demographic Model (MDM)" (contract AG-4-2107) with ICF Inc. is nearing completion. As an indicator of the MDM's potential, the Social Security Administration has contracted with ICF Inc. for simulations of the model as part of a report entitled, "Study of the Potential Economic and Fiscal Effects of the Investment of the Assets of the Social Security Old-Age and Survivors Insurance and Disability Insurance Trust Funds." The Social Security, Old Age and Survivors Insurance and Disability Insurance (OASDI) are projected to have large surpluses over the next 3 decades due to the 1983 Social Security Legislation. Unlike the Social Security Actuary's approach, the MDM can conduct economic analyses of the effects of this law on the national savings and capital accumulation, and the related effects on consumption, interest rates, and GNP. The analysis is complicated by the discretionary fiscal policy choices of the Federal Government which result in a wide range of outcomes.

"Household Formation and Housing," (contract AG-5-2106) has implemented the discrete/continuous Translog Model of Housing Demand. In this approach, households first decide the tenure or type of housing they wish to consume. Contingent on this choice, the second stage of the decision process is the determination of the quantity of housing services. The expected demands of individuals are obtained by summing across the conditional demands in all tenures in which the weights are the probabilities of choosing a specified housing alternative. Household formation will be developed from a demographic model of long-term trends. In-kind transfers for food, housing, and medical care will be incorporated into the econometric model.

Research Highlights for FY88

A model of consumer and health expenditures has been successfully developed and integrated into the NIA Macroeconomic-Demographic Model (MDM). The

consumer expenditures model disaggregates aggregate consumer expenditures into five components--food, health care, consumer goods, capital services, and consumer services. The health expenditures are disaggregated into types of expenditures--hospital, physician, dental, other health care professional, drugs, eyeglasses and appliances, and nursing home care. Demographic detail is provided on age, sex, race, family size, region, and urban-rural location. A third model selects a health insurance status. A projection of health expenditures is reported to the year 2050. Such a projection should not be considered a forecast of future events since it was impossible to factor in new policies such as the prospective payment system and the Medicare catastrophic insurance mechanism. The annual growth rate of total U.S. personal health expenditures is projected to slow down gradually from 5.8 percent in 1980 to 2.0 percent in 2020. Personal health expenditures as a ratio to GNP will increase about 3 percentage points from 1980 to 2050. The share going to hospitals will expand at the expense of the share going to nursing homes. The Medicare system is projected to expand considerably after the year 2000 and increase its share of total personal health expenditures. Direct patient payments and third-party payments are projected to remain stable through out the projection. Medicaid declines gradually with increasing income growth of the population. The most controversial part of the projection implies that health expenditures will not grow as fast as HCFA trend projections because of behavioral adjustments to the rising prices of health care. Such projections indicate the uncertainty that the future holds for the current U.S. health system.

In "Future Health Care Expenditures and Consumer Expenditures Under Alternative Scenarios" five scenarios are projected with the NIA MDM of health care and consumer expenditures. The five scenarios are a base case, higher population growth, higher elderly dependency growth, higher elderly dependency rate, and higher income growth. In the higher elderly dependency rate scenario, it is assumed that fertility rates decrease from their current levels (1.9 to 1.6), life expectancy increases over the base case, and net immigration falls. The elderly dependency rate is defined as the ratio of population age 65 and older to population age 20 to 64. The higher elderly dependency ratio results in 5.4 percent increase in per capita health expenditures, while nursing home expenditures, medicaid, and medicare expand. The major factor influencing health care expenditures is income. For example, personal health care expenditures are over 80 percent greater in 2050 for the higher income scenario than in the base case, although the total population and its distribution are held constant.

In "Demand for Health Insurance by the Elderly: A Microsimulation Model," by Drs. Lien-fu Huang, Teh-wei Hu and William S. Cartwright, the optimum coinsurance rate for Medigap policies is simulated. The results illustrate for the constant elasticity utility function with a risk aversion coefficient at 0.0005, the elasticity of medical care demand at -0.5, and the loading costs at 9 percent, without a subsidy, the average Medigap coinsurance rate is 0.78; and with the premium subsidy of 60 percent, the coinsurance rate drops to just 13 percent. The price elasticities of the demand for medigap insurance are estimated to be between -0.44 to -1.02. This study illustrates that more than half of the increase in medical expenditure resulting from an increase of Medigap premium subsidy from 0.35 to 0.60 are social welfare loss.

CONTRACT

Name and Number : ICF, Incorporated (NO1-AG-5-2106)

Title : Household Formation, Housing and the Aging Population

Date Contract Initiated: June 30, 1985

Total Cost of Contract : \$252,180

Objectives : The purpose of this contract is to investigate household formation and the interactions with the aging United States population and the economy.

Methods Employed : This work shall involve analysis of appropriate data bases and econometric modeling. The NIA Macroeconomic Demographic Model (MDM) shall be augmented by the resulting behavioral relations developed in the analysis. Thus, a method of integrating household formation with the MDM is a key task in this project. Another particularly important aspect is the interaction of housing and household formation. Because housing and household formation are so closely related, a housing model will be constructed and integrated with the NIA MDM. The resultant household formation model and the housing model will permit an examination of the implications of an aging population in the United States.

Significance to Biomedical Research: The NIA supports the MDM which permits study of the relationship between the economic status of the elderly and the national economy. As population aging continues through the 20th century and into the 21st century, the complicated mechanisms of economic dependency and related health effects must be continually studied. For example, the health and welfare of the elderly will be affected both by the evolution of the economy and the income security system. The MDM has recently been augmented by the development of health and consumer expenditure models.

Proposed Course : This work shall involve analysis of appropriate data bases and econometric modeling. The NIH MDM shall be augmented by the resulting behavioral relations developed in the analysis. Thus, a method of integrating household formation with the MDM shall be accomplished under this contract. Additionally, a housing model shall be constructed and integrated with the MDM. The resultant household formation model and the housing model shall permit an examination of the implications of an aging population in the United States.

CONTRACT

Name and Number : ICF, Incorporated (NO1-AG-4-2107)

Title : Updating and Revising the Macroeconomic-Demographic Model

Date Contract Initiated: September 26, 1984

Total Cost of Contract : \$253,046

Objectives : The objective is to update and revise the MDM. This will involve both re-estimation and other revisions to the equations and structure of the model in order to update the model from newly available data and from institutional changes in Federal programs. The end result will be an updated new base case for the computer simulation model that can be used for analysis of policy change and population aging. This work shall be consistent with the ongoing modeling.

Methods Employed : The NIA MDM is a complex computer simulation model. It consists of a large FORTRAN program that is over 7,000 lines long and has 43 sub-routines and a main program. The equations that make up this computer simulation model come from mathematical relations of the actuarial and the demographic sciences, as well as behavioral relations from economic science. The behavioral relations are statistically based equations that are estimated from underlying data bases. The equations are conceptually grouped into various models depicting key aspects of the economy. These models are the Population Model, the Macroeconomic Growth Model, the Labor Market Model, the Social Security Model, the Private and Public Employee Models, the Supplemental Security Income Model, and the Medicare Models. Health and consumer expenditures models were recently added.

Significance to Biomedical Research: The demographic structure of the U.S. population is aging. This has profound implications for the nation as an increasing number of elderly survive into older and older ages. The NIA MDM projects a 150 percent increase in those 65 and older from 1980 to 2050. This will affect Federal programs for both health and income security. In particular, health information shall be enhanced through this updating process so that critical aspects of population aging and health policy may be examined with more immediate policy relevance. Further, there will be immediate near term requirements for analyses of the social security system and other private pension systems.

Proposed Course : A new base population and adjustment factors derived from the 1980 Census of the U.S. population will be incorporated. An alternative base population shall be developed that is consistent with the Social Security projections. A new set of projections will be constructed for the base case consistent with Census and Social Security projections.

BIOMETRY OFFICE

In FY 1988 activities of the Biometry Office have evolved somewhat from what they were in FY 1987, with a number of changes having taken place in the structure of the overall Program and with more administrative responsibility having been assigned to Biometry Office staff. Mr. Foley and Mr. Everett have taken over as Project Officers for the contracts supporting the New Haven and Duke EPESE sites, respectively. While these new duties have necessarily taken some time away from analytical activities, emphasis on data management and data analysis for a variety of studies maintained by the EDB Program has persisted. Staff members have been heavily involved in numerous projects related not only to the EPESE, but also the NHANES Epidemiologic Follow-up Study (NHEFS), and the Survey of the Last Days of Life. Our liaison and consultative activities with other programs, institutes, and agencies has continued, primarily with the National Center for Health Statistics (NCHS) and other NIA programs and NIH institutes. In addition, some methodological studies have moved further toward completion and others into the planning and development stages. The NIA support for the National Mortality Followback Survey (AG-5-0057) is now complete and another interagency agreement was executed for support of an NCHS project for development of software for rigorous statistical analysis of complex sample survey data (AG-7-0108). The first phase of that project has now been completed.

Work on the EPESE Resource Data Book for the Duke site is now well underway, with preliminary tables having been produced for several of the chapters and some text now existing in draft form. The data tape from Duke arrived in near final form, enabling staff to begin preliminary work on the book at an early date. This publication will be produced utilizing an increased level of automation, including camera-ready personal computer graphics produced in-house and desk-top publishing of the text as well as computer-generated and automatically-typeset tables. Not only will this system be far less prone to error and less costly, but also more timely than with the first EPESE book, since there will be no requirement to have the typesetting done at the Government Printing Office.

Data management activities in other areas for the EPESE continue at a very high level. In addition to the semiannual submission of corrected data for the baseline survey, the first and second telephone follow-ups, the second in-home interview and endpoint data (mortality, hospitalizations, and nursing home stays), we are now collecting data that indicate follow-up status for every year of the study and the occurrence of endpoints. Submissions of data for the third telephone follow-up are also underway. Duke will soon submit its first telephone follow-up data. Also, additional requirements will be forthcoming regarding more rapid submissions of data tapes from the contractors which will add considerably to the workload of the data management staff. It will probably be necessary to stagger the arrival dates of data tapes in the future to allow sufficient time for review and editing by the staff.

All tape formats for EPESE not previously revised have been standardized in such a way that each location is following the same format for all common data items. This is the first of many steps required to begin to implement public release of the data. All data files now contain the same core information such as age and sex in the beginning of each record. In the files containing questionnaire data, the core section is followed by the common section

containing data which pertain to all the centers. Each file ends with a supplement of data unique to each center. All data are arranged by subject and the order of the subjects is the same for all files.

A new undertaking--an item file for the EPESE questionnaires--will soon be prepared by this office. This file will be ordered by subject as in the general tape formats and by item within subject categories. This file will also indicate each questionnaire in which the item appears. The item numbers will be the same as those on the formats, thus making it easy to find in the formats. This will be a major activity as thousands of questions are involved.

The programming staff has successfully installed 18 additional personal computers to make available personal computing power to every EDB staff member. In addition, enhancements have been made to two of the PC's for additional memory and speed to improve their efficiency for graphics and statistical computing. Further, the office has taken delivery on the IBM Personal System/2 Model 80 computer, considered by most to be the next generation in personal computing. As experience is gained with this powerful machine, we expect to be able to achieve much more in the way of sophisticated analysis and graphics work. It should be noted that the staff, especially Ms. Lafferty and Ms. Phillips, performed outstanding service in overseeing the handling of the PC's during the several office moves that took place this past winter. It is gratifying to see how quickly and easily the entire EDB staff has made the transformation to use of personal computers for most office functions.

EPESE data analysis procedures have begun to evolve from those that were being followed at this time a year ago. The committee structure has begun to give way to a simpler system of collaboration involving interested researchers among EDB staff and the four sites. Analyses in high priority areas are now being tracked by the new Project Officers and the investigators in an effort to expedite the writing of collaborative papers. Analyses are being prepared in such subject areas as mortality related to a variety of predictors, including physical functioning, blood pressure, smoking and alcohol use and other variables. Nursing home admissions, diabetes, cognitive functioning, drug use and other characteristics of the four populations are also being studied. Mr. Foley presented a paper on nursing home care at the 1987 Gerontological Society meeting. Additional analyses are underway to extend results reported last year on the effects of clusters of conditions on various outcomes in the EPESE (comorbidity) as well as individual conditions.

The EPESE Documentation Committee, chaired by Dr. Brock, has continued its work in standardizing documentation and data set specification for all EPESE data collection, editing, and processing activities. As mentioned above, new formats for data sets have been developed and communicated to the centers through the committee members. The committee has been working with Ms. Service, the new representative from the Duke study, to integrate existing procedures into the efforts of the Duke staff in their data preparation and submission activities to ensure compatibility with the other locations. The committee will also be working with the new Project Officers in an attempt to provide more timely data submissions and responses to feedback of those submissions from the EDB data management staff. With the transition from active data collection to surveillance activities following the 1988 in-home interview, some of these goals should be easier to achieve.

Biometry Office staff have continued activity in the analysis of data from NHEFS. Mr. Everett presented a paper on the accuracy of retrospectively reported body weight at the 1987 American Public Health Association meeting. He also collaborated in the writing of another paper presented at the APHA meeting. This paper concerned a reexamination of height, weight, gender, and age relationships in the combined NHANES I and II. He has submitted a paper on dietary patterns in the elderly for publication. This work was based on a professional service contract to establish compatible food groupings for the NHANES I and NHEFS dietary intake data. He also coauthored a paper on osteoarthritis and peptic ulcer which was presented at the 1988 meeting of the Society for Epidemiologic Research. Final drafts have been completed for the NHEFS book Health Status and Well-being of the Elderly for chapters on nutrition, arthritis, physical functioning, and cerebrovascular disease, with participation by Mr. Everett, Mr. Foley, Ms. Losonczy and Dr. Brock. Additional analyses are underway on relationship of functional health to dietary practices and adequacy; ideal body weight; body weight and mortality; and the relationship between aging, dietary and hematological factors and renal disease.

Ms. Losonczy has collaborated actively with Dr. White in the analysis of NHEFS data on risk factors for stroke and on mortality subsequent to stroke. In addition she has overseen the completion of professional services contracts to study dietary patterns and self-perceived health based on NHANES I and NHEFS data.

The analysis of data from the Survey of the Last Days of Life (AG-2-2137) has continued, moving beyond the basic description presented at the American Statistical Association meeting last summer. Questionnaire data have now been satisfactorily edited and cleaned and a paper is being prepared on the decline in physical, cognitive and sensory functioning in the last year of life. These results will be presented at the upcoming meeting of the American Statistical Association. Analysis is currently underway on transitions among nursing homes, hospitals and private residences involving episodes of care in the last 90 days of the decedents' lives. A draft paper is expected to be completed soon. Another area of analysis is a study of factors surrounding the changing presence of family and friends prior to death. This work will be carried out via a professional services contract with a family physician at the University of Illinois. Work is continuing on the editing of the data from hospitals and nursing homes that were contacted during the study, as well as the data on prescription medications for pain. As that work is completed, it will be possible to begin analysis of those data. It will be desirable to relate many of these characteristics to the underlying cause of death for the decedent as recorded on the death certificate. To facilitate these analyses a professional services contract was executed with the nosologist who has been coding the EPESE cause-of-death data to similarly code the underlying causes of death for these decedents. Finally, when the hospital data are satisfactorily edited some limited data on use and cost of services will be available for analysis in conjunction with data on utilization to be acquired from the Health Care Financing Administration.

The National Mortality Followback Survey data collection has now been completed, and editing and cleaning of the data is on schedule for a fall 1988 release of the data for analysis. This survey, supported by an interagency agreement with NCHS (AG-5-C057), is based on a sample of 20,000 death

certificates recorded during calendar year 1986 in the NCHS Current Mortality Sample. Mail questionnaires were sent to the next-of-kin of the deceased approximately 5 months after the date of death, with follow-up of nonrespondents by telephone or personal interview. Response rates for the survey have been in the 85 to 90 percent range for the next-of-kin data, a quite good response. The content of this study is similar in scope to the Survey of the Last Days of Life, particularly in regard to use of nursing homes and cognitive functioning in the last year of life. These data can be related to a variety of health characteristics of these decedents regarding use of services in the last year of life, and information available from the death certificate. We executed a small add-on to the interagency agreement to provide support for reinterviews of a sample of respondents for the purpose of estimating the reliability of the responses received, and to exercise quality control over the field data collection. We expect work on this data set to intensify as the data become available for analysis.

Analysis and reporting of data on aging have continued in other areas as well as the ones already mentioned. Dr. Guralnik, Dr. Brock, and Dr. Jacob Brody have published an article describing demographic characteristics of the older population in the U.S. in Advanced Geriatric Medicine, edited by F. I. Caird and J. Grimley Evans. Further, Dr. Brock has collaborated with Drs. Huntley, White and Cartwright on an article on the development of the EDB Program published in Epidemiology and Aging, edited by J. A. Brody and G. L. Maddox. Drs. Brod , Brock and Guralnik are beginning work on an update to the chapter on epidemiology for the next edition of the Handbook of the Biology of Aging, to be published by Van Nostrand Reinhold. Finally, Dr. Brock and Mr. Foley have contributed a chapter on the Survey of the Last Days of Life to be published in The Encyclopedia of Oncology, edited by Hans E. Kaiser.

Methodological work has continued in the Biometry Office, although in somewhat less intensity than in the past because of more involvement by the staff in administrative responsibilities. A final report and preliminary software have been received from the contractor on the project concerning regression analysis of complex survey data based on the 1986 interagency agreement with NICHD. We are beginning work with the NICHD Project Officer to evaluate the software and the methodology on some data sets taken from the NHANES and the NHEFS.

In a project related to the one on regression analysis, the development of a package of improved statistical software for analysis of complex sample survey data is continuing. A small interagency agreement with NCHS to support a contract for this project was executed in FY 1987. The results of the regression analysis contract (above) will be incorporated into the resulting software package as well as improved methods for conducting epidemiologic analyses on complex survey data in addition to standard NCHS analytical requirements. This package will be extremely useful in allowing more statistically rigorous analysis of data from several sources which involve complex sample surveys.

Because NIA was unable to allot its original commitment of funds to this project, however, there may be delays in completing the development of this package beyond the basic requirements of the contract. Unfortunately for EDB, this would limit the usefulness of the software to more standard analysis techniques and not allow for the expansion of the project into the areas of greatest potential use to the EDB.

Another area of continuing interest in methodology is the effect of missing responses in surveys. We have extended previous work in this area to a study of the use of prediction models for mortality (in the EPESE) which retain survey respondents with missing items for some of the predictor variables. This approach not only increases the power to detect differences, especially given the relatively small number of deaths observed in the EPESE, but it also alleviates a problem reported last year concerning the sex differences in mortality rates according to the amount and type of missing data among the predictors. A Monte Carlo study was conducted which compared prediction models which are based on cases with complete data only to models in which all subjects were left in the model, with indicator functions used to delineate the missing items. The results of this study, presented at the American Statistical Association meeting in San Francisco, showed that not only were there substantial disagreements between the retention models and the complete-case-only models, but that the retention models were correct a significantly greater proportion of the time. The conclusion one would draw from this study, limited as it is, is that clinically relevant results must not be based on complete-case-only analyses forcing speculation about nonresponse bias, particularly since incomplete data cannot be validated.

One other methodological area should be mentioned in this section. A proposal was made and has now received approval for an evaluation project to examine several methods of analyzing change in longitudinal data such as those arising from the EPESE. The project, due to be financed with 1 percent evaluation funds, will compare a variety of existing methods used by a number of researchers in the statistical literature. Among the methods to be studied are the random effects models of Laird and Ware in the biometrics literature, the structural equations models of Joreskog, the stochastic process models developed by Woodbury and Manton and the Grade of Membership models recently described by Manton and Singer. Other techniques may be included in the comparison if it is deemed that they may be potential competitors for the ones mentioned here. The objective of the study will be to find the most appropriate technique(s) for analyzing EPESE data over time not only from the standpoint of statistical properties, but also from the practical point of view; that is, methods which are feasible to apply and for which statistical software is either already available or can be developed in a straightforward manner for application by the epidemiologic community.

Other initiatives which will be described in more detail later in this sourcebook include a project to be funded by an interagency agreement from the Department of Transportation to investigate driving behavior of older persons in the EPESE populations. Two other projects involve contracts to provide computing services to expedite the analysis of EPESE data. One contract would provide for computing support to EDB epidemiologists' analysis of a variety of EPESE data sets on an as-needed basis when the regular workload of the programming staff precludes additional analytic work. The second, to be funded initially by a professional services contract, would support the development of data sets to be stored on an optical scanning device called a WORM (write-once-read-many) compact disk drive which would enable large EPESE data sets to be accessed by analysts directly from their personal computers without having to use the mainframe computer. This would allow for more timely production of statistical analyses and ease the workload of the programming staff.

Research Highlights for FY88

- o Analysis of EPESE mortality data has shown that although the ADL, Rosow-Breslau and Nagi physical function scales are all individually predictive of mortality at 3 years after baseline in each of the first three EPESE locations, when all three scales were used in the same statistical model, only the Rosow scale retained its significant relationship with mortality.
- o A Monte Carlo study of missing data patterns in the Iowa EPESE showed that mortality prediction models which retained participants with missing predictor variables do not always yield the same results as models using only those participants with complete data on the predictors. In addition, the study showed that when the models disagree, the retention models were correct in their predictions significantly more often than the complete-case-only analyses.
- o Analysis of physical functioning data in the NHEFS shows statistically significant relationships among morbidity, health perceptions, health behaviors and subsequent mortality and functional status. Men were shown to be less likely to be dysfunctioning than women, although men experienced higher mortality rates. Among predictors of dysfunction, arthritis was the most apparent, whereas cardiovascular and pulmonary diseases were most predictive of mortality. Perceived health status, smoking, activity level and exercise were all predictive of mortality among men, but only perceived health status predicted disability. For women, only perceived health status and smoking predicted mortality, whereas all of these variables except exercise predicted disability.
- o Analysis of NHANES I and II data has shown that, controlling for height and age in an ideal weight-for-height group, men have greater mean weights. Also, the data suggest an age-related decline in mean weight starting at ages 45 to 54 for men and 65 to 74 for women. Further, comparing men and women of the same height eliminates the apparent sex difference in mean weight. Finally, men in the 35 to 44 age group and women in the 55 to 64 age group have the greatest mean weights at similar heights and that these means are nearly identical.
- o A study of the accuracy of retrospectively reported body weight in the NHEFS showed that 10-year recall of body weight is very accurate for most individuals, some 65 percent being within 10 pounds of measured weight. Although there were no differences between men and women in the accuracy of recall in absolute terms, there is a tendency for more women to understate their previous weight than to overstate. No age effect was observed in the accuracy of weight recall, older individuals being as accurate as younger ones. Lastly, current weight has a strong influence on recall error in that the lightest individuals tend to overstate their previous weight, whereas the heaviest tend to understate.
- o A study of clusters or complexes of disease in the EPESE East Boston and Iowa locations has indicated higher rates of utilization of health care and mortality at two years' followup for those persons who had hypertension along with physical impairments and chronic conditions than for those individuals who had only one condition or impairment. These findings on comorbidity were more pronounced at older ages (75 to 84 and 85 and older)

and point out the importance of examining the total picture of health of an older individual as it is related to outcome measures. In future investigations involving more years of followup it will be important to identify risk factors for these clusters/complexes of disease in the evaluation of outcomes in these populations.

- o Analysis of data from the Survey of the Last Days of Life has been done for functional health on a typical day one year before death, one month before death, and the day before death. The highest rates for good functioning were in the area of mental status, where 51 percent of the decedents had no difficulty in either recognition or orientation on the day before death. Similarly high rates were reported for the ability to see and hear, but rates were much lower for good physical functioning (mobility, bathing, transferring and feeding). With regard to other conditions present during the lifetime of the decedent, a history of stroke or Alzheimer's disease was associated with less desirable trends for physical, mental and sensory functioning, whereas heart disease was associated with more desirable trends in functioning.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 06060 04 EDBP

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

National Mortality Followback Survey

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Dwight B. Brock, Ph.D

Chief, Biometry Office, EDBP, NIA

COOPERATING UNITS (if any)

National Center for Health Statistics

LAB/BRANCH

Biometry Office

SECTION

Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This survey is based on a sample of 20,000 death certificates recorded during calendar year 1986 in the NCHS Current Mortality Sample. Mail questionnaires are sent to the next-of kin of the deceased approximately 5 months after the date of death, with follow-up of nonrespondents by telephone or personal interview. In the first three quarters of data collection a response rate of 89 percent has been achieved. The data collection for this study will continue into FY 1988, and it is now estimated that a data tape will be made available to the EDB Program in the fall of 1988. A small add-on to the interagency agreement has been executed to provide support for a reinterview of a sample of responses for the purpose of estimating the reliability of the responses received, and to exercise quality control over the field data collection.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 06080 01 EDBP

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Complex Survey Analytical Software Development

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Dwight B. Brock, Ph.D, Chief, Biometry Office, EDBP, NIA

Lester R. Curtin, Chief, Statistical Methods Staff, ORM, NCHS

COOPERATING UNITS (if any)

National Center for Health Statistics

LAB/BRANCH

Biometry Office

SECTION

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TOTAL MAN-YEARS.

PROFESSIONAL.

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of this project is to support the development of a computer software package to tabulate and analyze sample survey data collected according to a multistage probability design. The package shall emphasize data analysis; that is, a user-friendly package will be provided that can be used to analyze sample survey data using statistically rigorous methodology, appropriately accounting for survey design complexities, such as stratification, clustering, unequal weighting and poststratification estimators. The package shall include procedures for (1) estimation of basic statistics and functions of those statistics, (2) generation of variances and covariances for those basic statistics and functions, (3) variance components for each stage of selection, and (4) statistical analysis, including simple hypothesis tests, analysis of variance by the general linear model, logistic regression, and survival analysis using the Cox proportional hazards model.

CONTRACT

Name and Number : DMH ASSOCIATES, INC. (NO1-AG-2-2137)

Title : Survey of the Last Days of Life

Date Contract Initiated: September 30, 1982

Total Cost of Contract : \$443,576

Objectives : The purpose of this project is to collect descriptive data on the last days of life for a community sample of persons age 65 and older whose deaths occurred in a one year period. In addition to providing specific data on basic events and circumstances surrounding death, the study provides lifetime prevalence data for a set of conditions related to, but not necessarily causing death.

Methods Employed : A sample of death certificates will be selected over a period of one year in Fairfield County, Connecticut. Retrospective information concerning the decedent's last days of life will be obtained in a face-to-face interview with an informant identified from information contained on the death certificate. Follow-up information will be obtained from medical sources identified by the informant for those cases in which it is appropriate.

Major Findings : Among lifetime period prevalence rates in the sample of decedents were 6 percent with a report of blindness, 8 percent with deafness and slightly more than 8 percent with a reported physician diagnosis of Alzheimer disease or other types of dementia. Other findings showed that more than half the deaths took place at a hospital, approximately one-fifth at home, and the remainder at other residential settings such as nursing home or hospice. More than half the decedents were reported to have died in their sleep and more than 90 percent saw various members of their families in the last three days of life. More than half the decedents were reported to have been in good or excellent health one year before death, a figure that declined to one-fourth the month before death and one-eighth the day before death occurred.

Significance to Biomedical Research: A considerable body of literature exists in the geriatric and psychological fields as well as in the lay press about dying. Yet specific data about basic events associated with dying are lacking--such as who dies peacefully in his/her sleep, who dies in great pain, what persons are present at the time of death, who dies after a long illness with full awareness of his impending demise, and who dies suddenly with no warning. Further, the proportion of the dying who need and actually receive pain medication is unknown. The study provides an opportunity to obtain epidemiological data on the numbers of persons affected by the major health conditions that confront the dying elderly as well as the lifetime likelihood of certain events and conditions such as blindness, deafness, dementia, hip fracture, and others.

Proposed Course : Preliminary data was presented at a conference entitled, "Death on Your Balance Sheet: Costs and Choices in Terminal Care for the Elderly" at the University of Hartford in Connecticut. A paper relating trends in health statistics and functioning to lifetime history of selected medical diagnoses was presented at the American Statistical Association meeting. Once the final checking of the data is complete, analyses will be conducted in several content areas including the circumstances surrounding death, transitions between home and various health care settings in the last 3 months of life, decline in physical and cognitive function and presence of symptoms in the last year of life, use of pain medications in the last month of life, and lifetime period prevalence of conditions associated with dying, but not necessarily causing death. In addition, analyses will be conducted on economic variables collected for those decedents who spent time in a hospital or nursing home in the last month of life.

1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12. 13. 14. 15. 16. 17. 18. 19. 20. 21. 22. 23. 24. 25. 26. 27. 28. 29. 30. 31. 32. 33. 34. 35. 36. 37. 38. 39. 40. 41. 42. 43. 44. 45. 46. 47. 48. 49. 50. 51. 52. 53. 54. 55. 56. 57. 58. 59. 60. 61. 62. 63. 64. 65. 66. 67. 68. 69. 70. 71. 72. 73. 74. 75. 76. 77. 78. 79. 80. 81. 82. 83. 84. 85. 86. 87. 88. 89. 90. 91. 92. 93. 94. 95. 96. 97. 98. 99. 100.

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